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# AMERICAN JOURNAL OF OPHTHALMOLOGY



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bubbles into the anterior chamber of  
human eye-bank eyes using viscoelastic  
solution during phacoemulsification.*

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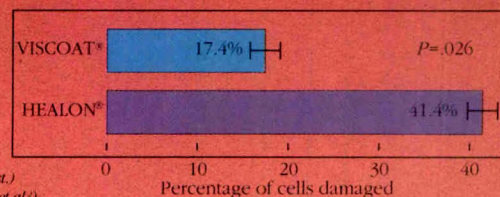
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(Adapted from Glasser DB et al<sup>2</sup>)



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## protection during phaco

Please see next page for summary of VISCOAT product information.

#### References

<sup>1</sup> Craig MT, Olson RJ, Mamalis N, Olson RJ. Air bubble endothelial damage during phacoemulsification in human eye bank eyes: The protective effects of Healon and Viscoat. *J Cataract Refract Surg.* 1990;16:597-602.

<sup>2</sup> Glasser DB, Katz HR, Boyd JE, Langdon JD, Shobe SL, Peiffer RL. Protective effects of viscous solutions in phacoemulsification and traumatic lens implantation. *Arch Ophthalmol.* 1989;107:1047-1051.

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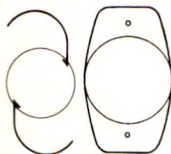
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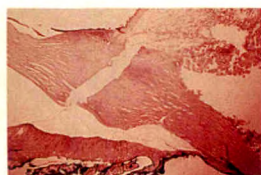


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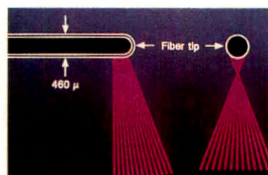
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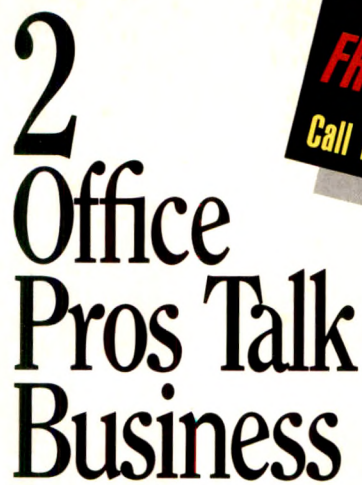
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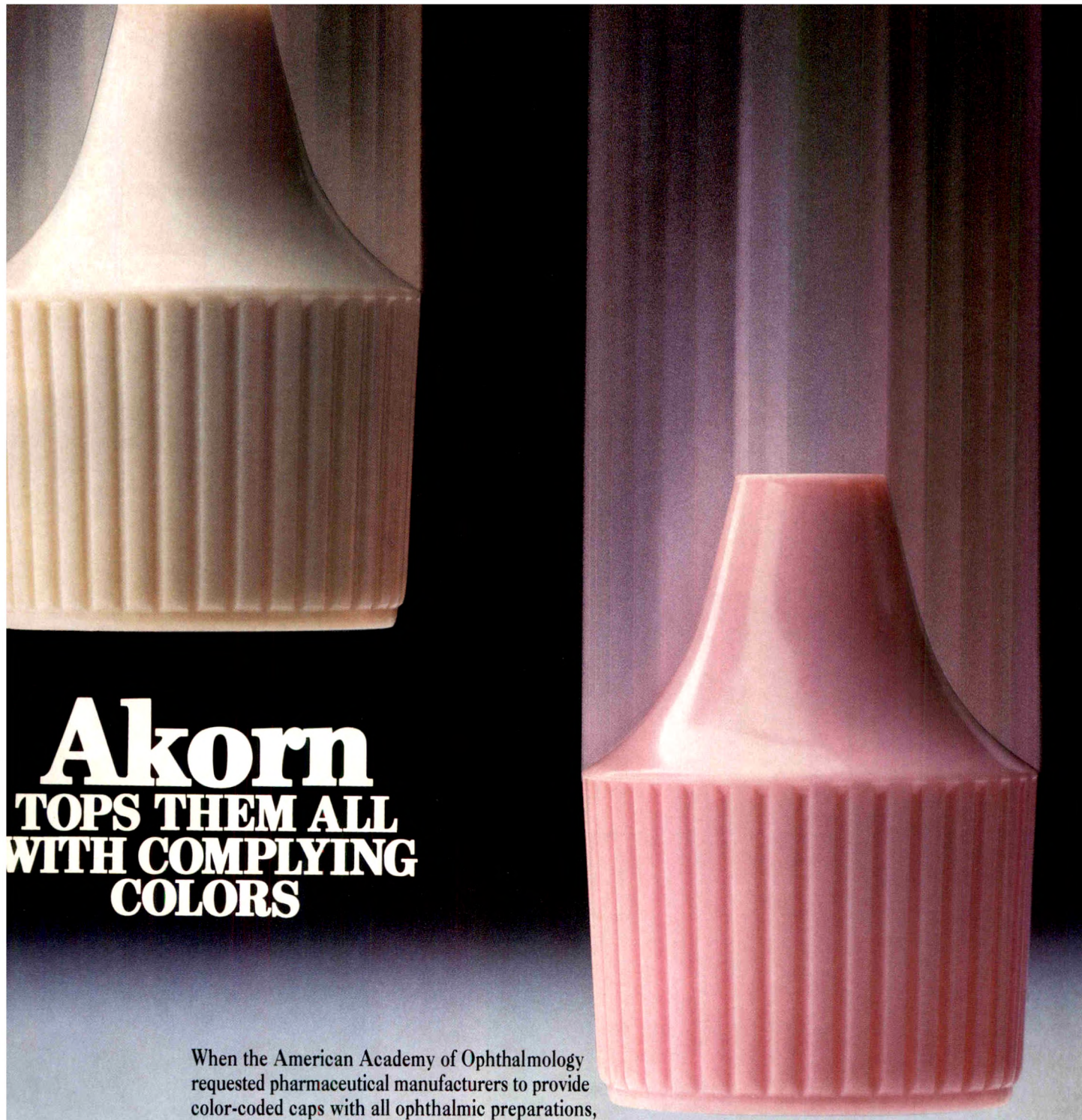
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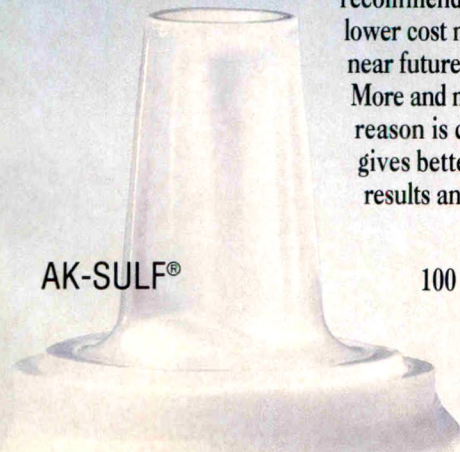


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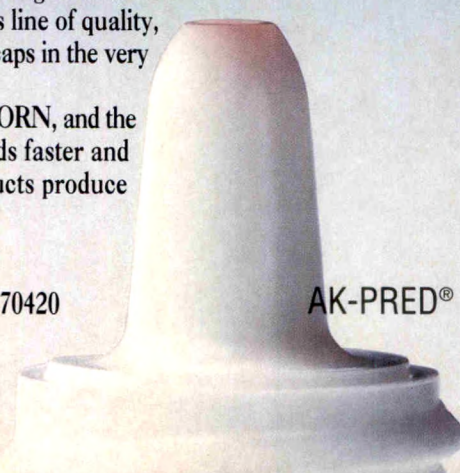
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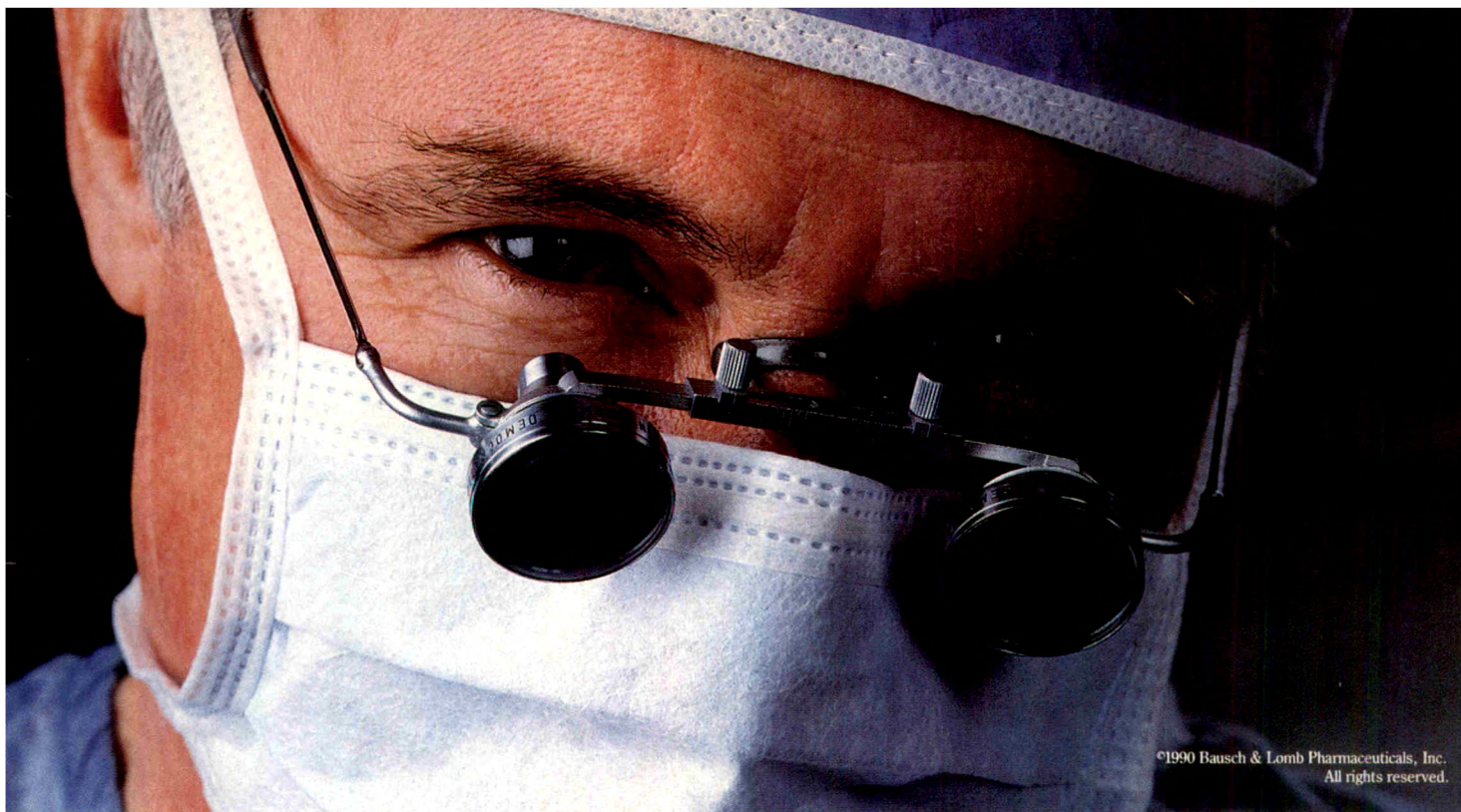
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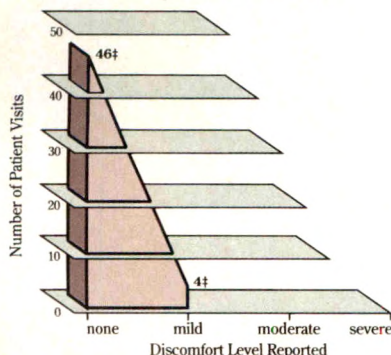


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*For POAG and ocular hypertensive  
patients where treatment is indicated*

## The S is for Strength

### Strength of drug delivery

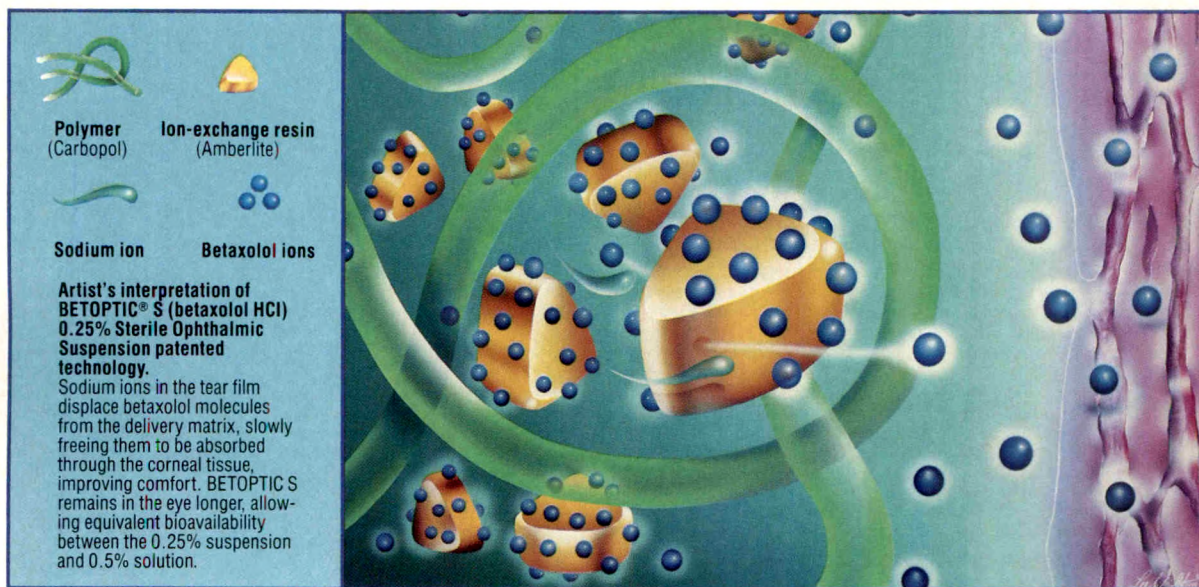
- Patented technology slows release and increases retention of drug in the eye
- The amount of betaxolol delivered to the aqueous humor by the 0.25% suspension is equal to that delivered by the 0.5% solution
- Efficacy equivalent to 0.5% solution has been demonstrated in clinical trials

### Strength of improved comfort

- Active drug is released more slowly to the cornea, resulting in improved patient comfort

### Strength of beta-1\* safety

- Offers the safety advantages of a selective ocular beta-blocker
- Does not significantly compromise heart rate or pulmonary function
- CNS side effects are rarely reported



\*Beta-1 selectivity is not absolute.

BETOPTIC<sup>®</sup> S Sterile Ophthalmic Suspension has produced minimal effects in patients with reactive airway disease; exercise caution in treating patients with excessive restriction of pulmonary function. Asthmatic attacks and pulmonary distress have been reported during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol have not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta-blockers cannot be ruled out.

Contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, overt cardiac failure, or hypersensitivity to any component of this product. Use caution in treating patients with a history of cardiac failure, heart block, and patients receiving adrenergic psychotropic drugs or catecholamine-depleting drugs such as reserpine. Observe patients receiving an oral beta-blocker and BETOPTIC<sup>®</sup> S suspension for possible additive effect on known systemic effects of beta-blockade.

PLEASE SEE BRIEF SUMMARY OF PRESCRIBING INFORMATION ON THE NEXT PAGE.

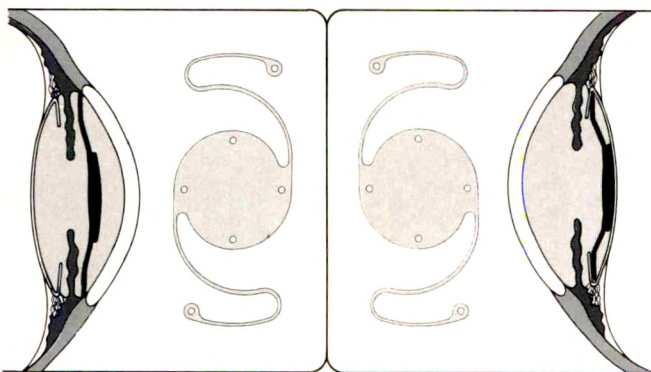
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SPA 35/58

## THE 1992 DUKE UNIVERSITY ADVANCED VITREOUS SURGERY COURSE APRIL 23-25, 1992 Duke University, Durham, North Carolina

This course is designed for the vitreo-retinal surgeon with experience. New developments in instrumentation and techniques will be presented with emphasis placed on detailed discussion of techniques and the outlining of problem areas. In order to stimulate the exchange of experiences audience participation will be encouraged and extensive discussion periods provided.

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### BETOPTIC® S (betaxolol HCl) 0.25% as base Sterile Ophthalmic Suspension

**DESCRIPTION:** BETOPTIC S Ophthalmic Suspension 0.25% contains betaxolol hydrochloride, a cardio-selective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation.

**INDICATIONS AND USAGE:** BETOPTIC S Ophthalmic Suspension 0.25% has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and ocular hypertension. It may be used alone or in combination with other intraocular pressure lowering medications.

**CONTRAINDICATIONS:** Hypersensitivity to any component of this product. BETOPTIC S Ophthalmic Suspension 0.25% is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

**WARNING:** Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents. BETOPTIC S Ophthalmic Suspension 0.25% has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S Ophthalmic Suspension 0.25% should be discontinued at the first signs of cardiac failure.

**PRECAUTIONS: General: Diabetes Mellitus.** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrotoxicosis.** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

**Muscle Weakness.** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

**Major Surgery.** Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. **Pulmonary.** Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. **Drug Interactions:** Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. **Pregnancy: Pregnancy Category C.** Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS: Ocular:** In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, edema and anisocoria. **Systemic:** Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include: **Cardiovascular:** Bradycardia, heart block and congestive failure. **Pulmonary:** Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure. **Central Nervous System:** Insomnia, dizziness, vertigo, headaches, depression, and lethargy. **Other:** Hives, toxic epidermal necrolysis, hair loss, and glossitis.

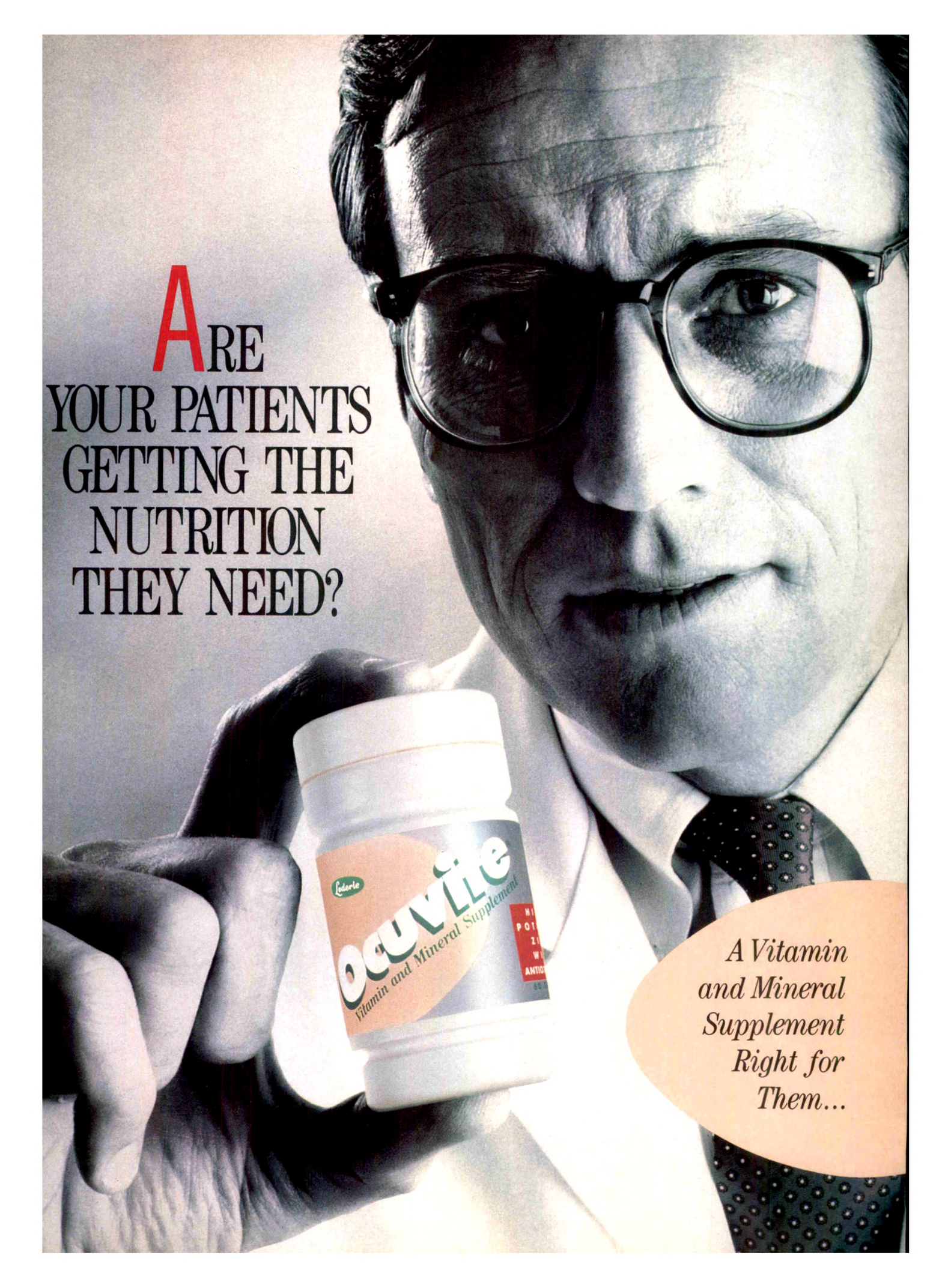
**OVERDOSAGE:** No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. A topical overdose of BETOPTIC S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

**CAUTION: Federal (USA) Law Prohibits Dispensing Without a Prescription.**  
U.S. Patent Nos. 4,252,984; 4,311,708; 4,342,783; 4,911,920.

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Vitamin and Mineral Supplement

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### IF YOUR PATIENTS ARE NUTRITIONALLY DEFICIENT...

A recent survey of the dietary habits of Americans revealed that intake levels of many essential minerals were below the low end of the Estimated Safe and Adequate Daily Dietary Intake range, and represented less than 80% of the US RDA! Older Americans, in particular, are at risk of low intakes in these micronutrients, especially copper and zinc! Another nationwide study concluded that a substantial portion of older Americans consumed nutritionally inadequate diets.<sup>2</sup>

### HERE'S A SUPPLEMENT RIGHT FOR THEM

OCUVITE has been designed to provide nutritional support for your patients. Its unique formulation includes 40 mg of elemental zinc as zinc oxide, the most concentrated form of zinc.\* That's 267% of the US RDA—more zinc than any leading multivitamin/multimineral product.

OCUVITE also contains 100% of the US RDA for the antioxidant vitamins C, E, and A (as beta carotene), and copper, as well as selenium, a mineral with antioxidant activity.



### REASONABLY PRICED

Less expensive than other leading multivitamin supplements,<sup>3</sup> OCUVITE has been priced with the elderly patient's budget in mind.

\*Zinc oxide contains more elemental zinc than any other zinc salt (ie: zinc sulfate or zinc gluconate).

### FORMULATED WITH ESSENTIAL MICRONUTRIENTS

Micronutrient	Zinc 40mg (elemental)	Vitamin C 60mg	Vitamin E 30 IU	Vitamin A 5000 IU (as Beta Carotene)	Copper 2mg (elemental)	Selenium 40mcg
Percent US RDA for Adults	267%	100%	100%	100%	100%	No US RDA established
Micronutrient Sources in Balanced Diets	Oysters, red meat, liver, soybeans, spinach, sunflower seeds	Citrus fruits, tomatoes	Eggs, organ meats, wheat germ, dark green vegetables, legumes	Dairy products, green and yellow fruits and vegetables, fish liver oil	Legumes, organ meats, seafood, nuts	Eggs, garlic, leafy green vegetables, liver, seafood, bran

**RECOMMENDED INTAKE:** Adults: One tablet, one or two times daily or as directed by physician.

**References:** 1. Pennington JAT, Young BE, Wilson DB, Johnson RD, Vanderveen JE. Mineral content of foods and total diets: The Selected Minerals in Foods Survey, 1982 to 1984. *J Am Diet Assoc.* 1986;86:876-878. 2. Fanelli MT, Steinhagen KJ. Characterizing consumption patterns by food frequency methods: core foods and variety of foods in diets of older Americans. *J Am Diet Assoc.* 1985;85:1570-1576. 3. *Red Book* \* Update. Oradell, NJ. Medical Economics Co Inc, 1990;July:48.

The uniquely-shaped tablet design is a registered trademark.

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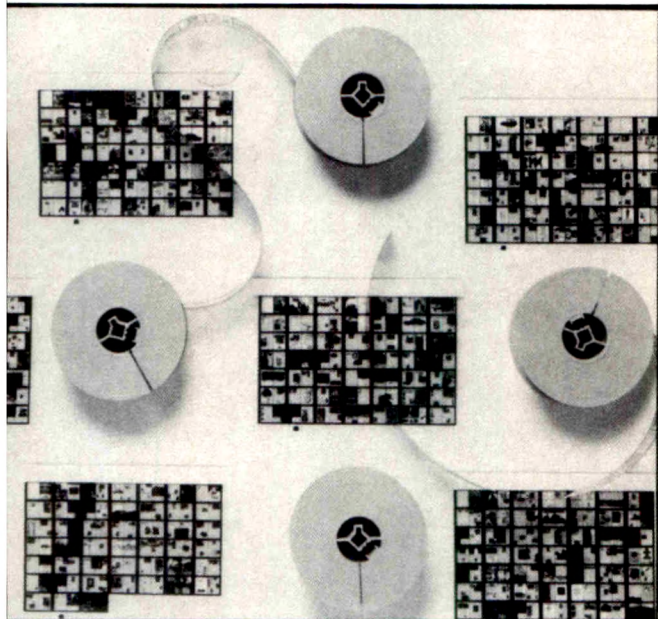
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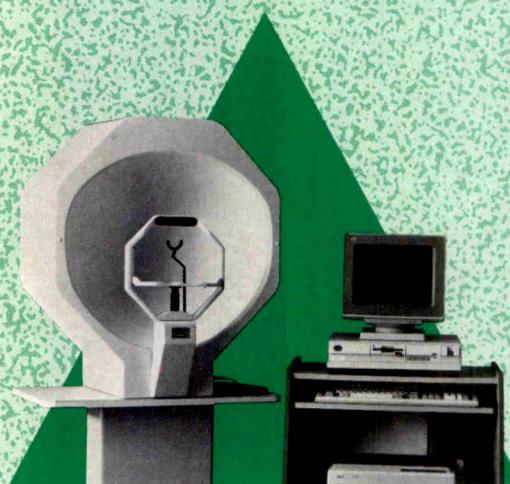
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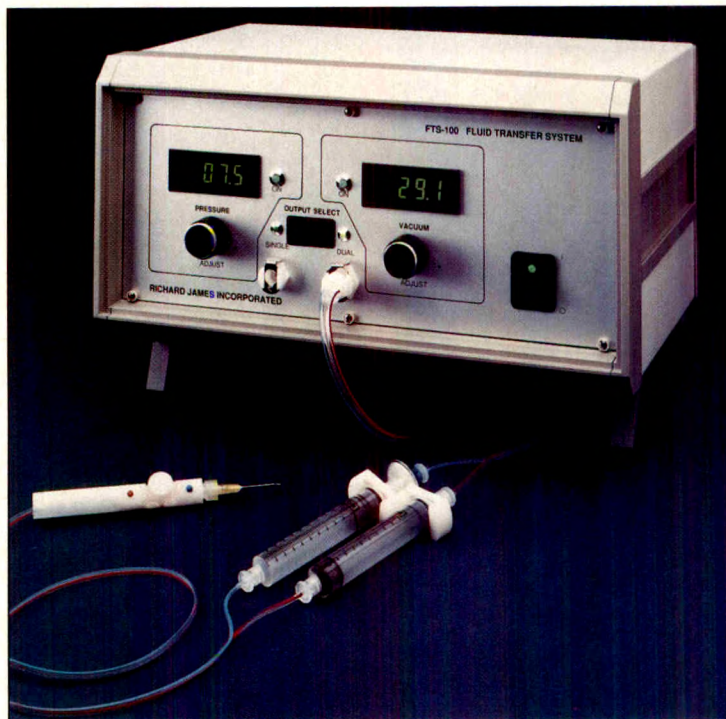
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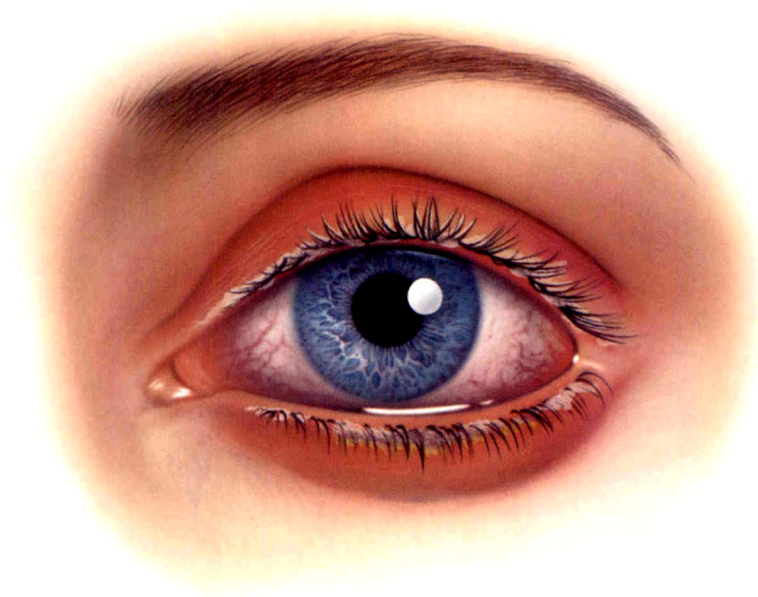
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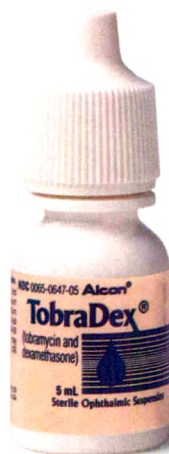




**THE RELIEF OF  
OCULAR INFLAMMATION  
AND ACCOMPANYING INFECTION  
CAN BE SUMMED UP IN ONE WORD.**



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TOBRADEX® (tobramycin 0.3% and dexamethasone 0.1%) is the combination you know and trust for relief of ocular inflammation and accompanying infection. First, TOBRADEX offers dexamethasone alcohol for decisive control of inflammation in the hospital and in the office. Second, it offers you all the advantages of TOBREX® (tobramycin 0.3%),



the most widely prescribed ocular antibiotic worldwide. Through bactericidal activity, this broad spectrum antibiotic destroys common ocular pathogens.

So next time you need an anti-inflammatory and anti-infective combination, sum it up in one word. Prescribe TOBRADEX.

# TOBRADEX®

(tobramycin 0.3% and dexamethasone 0.1%)  
STERILE OPHTHALMIC SUSPENSION/OINTMENT

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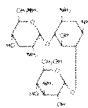
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## TobraDex®

(Tobramycin and Dexamethasone)  
Sterile Ophthalmic Suspension and Ointment

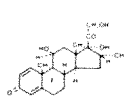
**DESCRIPTION:** TOBRADEX® (Tobramycin and Dexamethasone) Ophthalmic Suspension and Ointment are sterile, multiple dose antibiotic and steroid combinations for topical ophthalmic use. The chemical structures for tobramycin and dexamethasone are presented below.



Tobramycin

Empirical Formula:  $C_{18}H_{37}N_5O_9$   
Chemical Name:

0-3-Amino-3-deoxy- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-O-[2,6-dia-mino-2,3,6-trideoxy- $\alpha$ -D-ribo-hexopyranosyl-(1 $\rightarrow$ 6)]-2-de-oxyl-L-streptamine



Dexamethasone

Empirical Formula:  $C_{22}H_{35}F_5O_6$   
Chemical Name:

9-Fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\alpha$ -methylpregna-1,4-diene-3,20-dione

Each mL of TOBRADEX® Suspension contains Active: Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). Preservative: Benzalkonium Chloride 0.01%, Inactive: Tyrokolol, Edetate Disodium, Sodium Chloride, Hydroxyethyl Cellulose, Sodium Sulfate, Sulfuric Acid and/or Sodium Hydroxide (to adjust pH) and Purified Water.

Each gram of TOBRADEX® Ointment contains Active: Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). Preservative: Chlorobutanol 0.5%, Inactive: Mineral Oil and White Petrolatum.

**CLINICAL PHARMACOLOGY:** Corticosteroids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticosteroids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibitor is considered to be clinically significant. Dexamethasone is a potent corticoid. The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococcus, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains; Streptococcus, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*; Pseudomonas aeruginosa, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, and *Acinetobacter calcoaceticus* (*Herellea vaginacalis*) and some *Neisseria* species.

Bacterial susceptibility studies demonstrate that in some cases *Moraxella lacunata* and *Acinetobacter calcoaceticus* remain susceptible to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

No data are available on the extent of systemic absorption from TOBRADEX® Ophthalmic Suspension or Ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. If the maximum dose of TOBRADEX® Ophthalmic Suspension is given for the first 48 hours (two drops in each eye every 2 hours) and complete systemic absorption occurs, which is highly unlikely, the daily dose of dexamethasone would be 2.4 mg. The usual physiologic replacement dose is 0.75 mg daily. If TOBRADEX® Ophthalmic Suspension is given after the first 48 hours as two drops in each eye every 4 hours, the administered dose of dexamethasone would be 1.2 mg daily. The administered dose for TOBRADEX® Ointment in both eyes four times daily would be 0.4 mg of dexamethasone daily.

**INDICATIONS AND USAGE:** TOBRADEX® Ophthalmic Suspension and Ointment are indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from radiation, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: Staphylococcus, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains; Streptococcus, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*; *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, and *Acinetobacter calcoaceticus* and some *Neisseria* species.

**CONTRAINDICATIONS:** Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

The use of this combination is always contraindicated after uncomplicated removal of a corneal foreign body.

**WARNINGS:** NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction does occur, discontinue use.

Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

### PRECAUTIONS

**General.** The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

**Information for Patients:** Do not touch dropper or tube tip to any surface as this may contaminate the contents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

**Pregnancy Category C.** Corticosteroids have been found to be teratogenic in animal studies. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy. Reproduction studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well-controlled studies in pregnant women. TOBRADEX® Ophthalmic Suspension and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers.** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, a decision should be considered to discontinue nursing temporarily while using TOBRADEX® Ophthalmic Suspension or Ointment.

**Pediatric Use.** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing.

**Secondary Infection.** The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

**DOSE AND ADMINISTRATION: Suspension.** One or two drops instilled into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, the dosage may be increased to one or two drops every two (2) hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely. **Ointment:** Apply a small amount (approximately 1/2 inch ribbon) into the conjunctival sac(s) up to three or four times daily.

TOBRADEX® Ophthalmic Ointment may be used at bedtime in conjunction with TOBRADEX® Ophthalmic Suspension used during the day. Not more than 20 mL or 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

**HOW SUPPLIED:** Sterile ophthalmic suspension in 2.5 mL (NDC 0065-0647-25) and 5 mL (NDC 0065-0647-05) DROP-TAINER® dispensers. Sterile ophthalmic ointment in 3.5 g ophthalmic tube (NDC 0065-0648-35).

**STORAGE:** Store at 46° to 80°F (8° to 27°C).

Store suspension upright and shake well before using.

**CAUTION:** Federal (USA) law prohibits dispensing without prescription. Patent pending.

## BETOPTIC® S (betaxolol HCl) 0.25% as base Sterile Ophthalmic Suspension

**DESCRIPTION:** BETOPTIC® S Ophthalmic Suspension 0.25% contains betaxolol hydrochloride, a cardio-selective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation.

**INDICATIONS AND USAGE:** BETOPTIC® S Ophthalmic Suspension 0.25% has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and ocular hypertension. It may be used alone or in combination with other intraocular pressure lowering medications.

**CONTRAINDICATIONS:** Hypersensitivity to any component of this product. BETOPTIC® S Ophthalmic Suspension 0.25% is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

**WARNING:** Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents. BETOPTIC® S Ophthalmic Suspension 0.25% has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC® S Ophthalmic Suspension 0.25% should be discontinued at the first signs of cardiac failure.

**PRECAUTIONS: General: Diabetes Mellitus.** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrotoxicosis.** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

**Muscle Weakness.** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

**Major Surgery.** Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. **Pulmonary.** Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. **Drug Interactions:** Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC® S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC® S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. **Pregnancy: Pregnancy Category C.** Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women.

BETOPTIC® S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC® S Ophthalmic Suspension 0.25% is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS: Ocular:** In clinical trials, the most frequent event associated with the use of BETOPTIC® S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, edema and anisocoria. **Systemic:** Systemic reactions following administration of BETOPTIC® S Ophthalmic Suspension 0.25% or BETOPTIC® Ophthalmic Solution 0.5% have been rarely reported. These include: **Cardiovascular:** Bradycardia, heart block and congestive failure. **Pulmonary:** Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure. **Central Nervous System:** Insomnia, dizziness, vertigo, headaches, depression, and lethargy. **Other:** Hives, toxic epidermal necrolysis, hair loss, and glossitis.

**OVERDOSAGE:** No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. A topical overdose of BETOPTIC® S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

**CAUTION: Federal (USA) Law Prohibits Dispensing Without a Prescription.**

U.S. Patent Nos. 4,252,984; 4,311,708; 4,342,783; 4,911,920.

**Alcon**  
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FORT WORTH, TEXAS 76134

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Fort Worth, Texas 76134



# The eyes can be windows to a lot more than the soul.

Some of the most poetic passages throughout history have been written about the eyes.

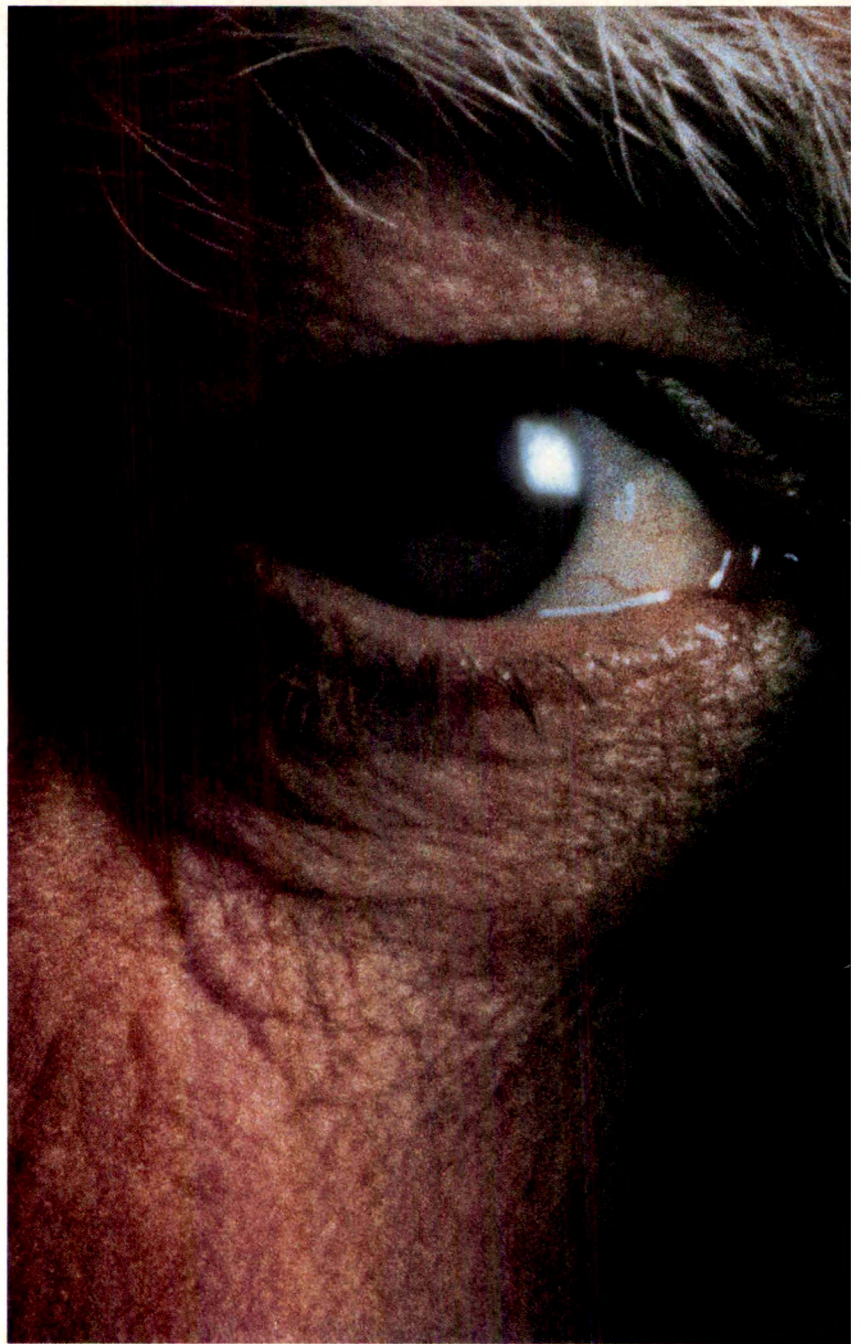
But this isn't one of them.

## Ocular beta blockers can affect more than the eyes.

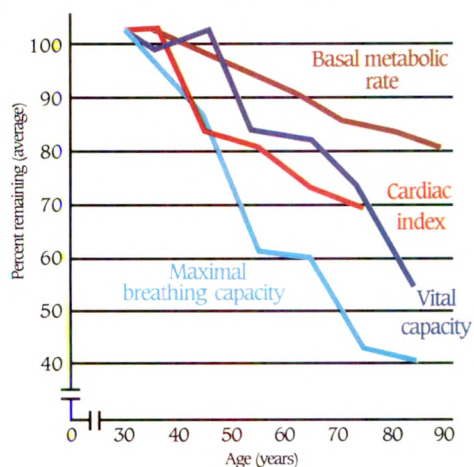
Unfortunate, but true.

Minutes after a single dose of an ocular beta blocker, the drug is detectable in the plasma of most individuals.<sup>1</sup>

That's important when you consider that most glaucoma patients are elderly. With age comes a normal decline in physiologic function and increased susceptibility to systemic disease.<sup>2</sup> And concomitant systemic medication increases the likelihood of adverse drug reactions.<sup>2</sup>



Loss of efficiency with age of several human physiologic functions.<sup>3</sup>



With BETOPTIC®S (betax HCl) you can expect long-term maintenance of IOP reduction.<sup>4</sup> A superior pulmonary safety profile.<sup>5</sup> Minimal cardiovascular effects.<sup>6</sup> And very low incidence of reported systemic side effects, including CNS effects.<sup>4</sup>

Doesn't it make sense to consider BETOPTIC S when treating the elderly glaucoma patient?





BETOPTIC® S Sterile Ophthalmic Suspension has produced minimal effects in patients with reactive airway disease; exercise caution in treating patients with excessive restriction of pulmonary function. Asthmatic attacks and pulmonary distress have been reported during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol have not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out.

Contraindicated in patients with sinus bradycardia, greater than a first-degree atrioventricular block, cardiogenic shock, overt cardiac failure or hypersensitivity to any component of this product. Use caution in treating patients with a history of cardiac failure or heart block.

Observe patients receiving an oral beta blocker and BETOPTIC S Suspension for potential additive effect on known systemic effects of beta blockade. Exercise caution in patients receiving catecholamine-depleting drugs such as reserpine and adrenergic psychotropic drugs.

BETOPTIC S Suspension has been well tolerated in a majority of patients. Discomfort of short duration upon instillation may be experienced. Systemic reactions have been reported rarely and a complete listing appears in the prescribing information.

#### References:

1. Givens KT, Lee DA. Topical beta blockers for glaucoma: what clinicians should know. *Geriatric Medicine Today*. 1989;8:105-113.
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4. Data on file, Alcon Laboratories, Inc.
5. Schoene RB, et al. Effects of topical betaxolol, timolol and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol*. 1984;97:86-92.
6. Atkins JM, et al. Cardiovascular effects of topical beta blockers during exercise. *Am J Ophthalmol*. 1985;99:173-175.

\*Beta-1 selectivity is not absolute.



**Betoptic® S**  
(betaxolol HCl) Sterile Ophthalmic Suspension, 0.25%

The beta blocker with a technological difference.

Please see page 19 for brief summary of prescribing information.

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OPHTHALMIC

Alcon Laboratories, Inc.  
Fort Worth, Texas 76134



# COLOR BAR™

# Schirmer Tear Test

Standardized Sterile Strips

Patent No. 5,006,310

A blue COLOR BAR with an FDA approved dye is imprinted on each strip that travels the tear flow and leaves a soft blue easy to read, vignette on the millimeter scale preprinted on each strip. Each sterile sealed clear pouch contains two strips, one with "R" and one with "L" indicating right or left eye printed at the bottom. These strips may also be attached to the patients record for future reference.

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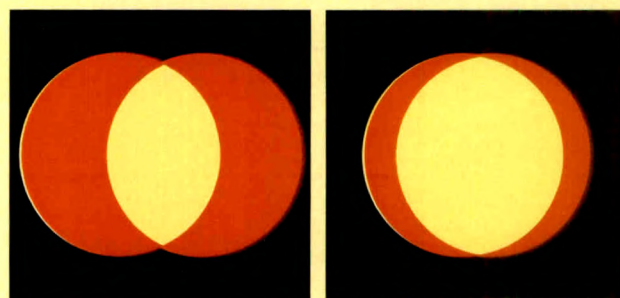
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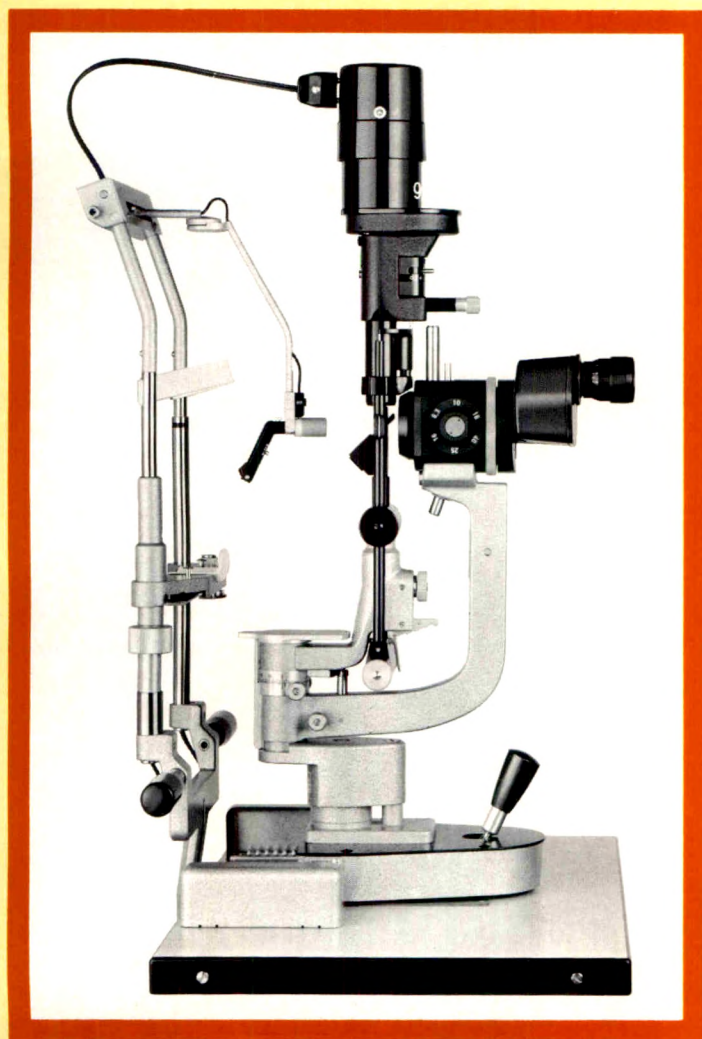
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What is the Stereo-Variator?

The result of the latest innovative thinking from Haag-Streit, it is a small control unit inserted in the superb new 900<sup>®</sup> BQ slit lamp microscope. With it, stereoscopic viewing of the deep vitreous and the retina may be obtained over a larger binocular field by simply switching the Stereo-Variator to a narrower imaging angle, from 13° to 4.5°. Examination is possible through small pupils or in high myopia, and even the endothelial cells may be viewed binocularly with consequent improved acuity.

The brilliant crystal-clear contrast of the 900<sup>®</sup> BQ microscope is retained throughout its whole magnification range of 6.3×, 10×, 16×, 25×, and 40×, all without changing the converging eye-pieces. The examiner remains at ease in the natural condition for viewing a near object, so is predisposed to receive a stereoscopic image.

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# ACHROMYCIN® Tetracycline HCl

OPHTHALMIC OINTMENT 1%, OPHTHALMIC SUSPENSION 1%

**NOT YOUR  
TYPICAL TOPICAL**

## REFERENCES:

1. Bialasiewicz AA, John GJ. Epidemiology of chlamydial eye diseases in a mixed rural/urban population of West Germany. *Ophthalmology*. 1986;93:757-762.
2. Walsh JB, Gold A (editorial consultants). *Physicians' Desk Reference for Ophthalmology*®. 16 ed. Oradell, NJ: Medical Economics Co; 1988.
3. Havener WH. *Ocular Pharmacology*. 5 ed. St Louis, MO: The CV Mosby Co; 1983:195,198.
4. Newell FW. *Ophthalmology: Principles and Concepts*. 5 ed. St Louis, MO: The CV Mosby Co; 1986:129,442.
5. Tabbara KF, Hyndiuk RA, eds. *Infections of the Eye*. Boston, MA Little, Brown & Co; 1986:215-16,414-415,431-33.
6. Fedukowicz HB, Stenson S. *External Infections of the Eye*. 3 ed. Norwalk, Conn: Appleton-Century-Crofts; 1985:96.

## ACHROMYCIN® Tetracycline Hydrochloride

Ophthalmic Ointment, USP, 1% Sterile

**DESCRIPTION:** ACHROMYCIN OPHTHALMIC OINTMENT, USP, STERILE contains 10 mg of tetracycline hydrochloride per gram with Light Mineral Oil, White Petrolatum and Anhydrous Lanolin as inactive ingredients.

Chemically, ACHROMYCIN tetracycline hydrochloride is: [4S-(4a,4aa,5aa,6b,12aa)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride.

**INDICATIONS:** For the treatment of superficial ocular infections susceptible to ACHROMYCIN.

For prophylaxis of ophthalmia neonatorum due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. The Centers for Disease Control (U.S.P.H.S.) and the Committee on Drugs, the Committee on Fetus and Newborn, and the Committee on Infectious Diseases of the American Academy of Pediatrics recommend 1 percent silver nitrate solution in single-dose ampoules or single-use tubes of an ophthalmic ointment containing 0.5 percent erythromycin or 1 percent tetracycline as "effective and acceptable regimens for prophylaxis of gonococcal ophthalmia neonatorum."<sup>1</sup> (For infants born to mothers with clinically apparent gonorrhea, intravenous or intramuscular injections of aqueous crystalline penicillin G should be given: a single dose of 50,000 units for term infants or 20,000 units for infants of low birth weight. Topical prophylaxis alone is inadequate for these infants.)

The following organisms have demonstrated susceptibility to ACHROMYCIN:

<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
<i>Streptococci</i> including	<i>Neisseria species</i>
<i>Streptococcus pneumoniae</i>	<i>Chlamydia trachomatis</i>

When treating trachoma, a concomitant oral tetracycline is helpful.

Other organisms not known to cause superficial eye infections, but with demonstrated susceptibility to ACHROMYCIN, have been omitted from the above list.

ACHROMYCIN does not provide adequate coverage against:

<i>Haemophilus influenzae</i>	<i>Pseudomonas aeruginosa</i>
<i>Klebsiella/Enterobacter species</i>	<i>Serratia marcescens</i>

**CONTRAINDICATIONS:** This product is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

**PRECAUTIONS:** The use of antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken.

**ADVERSE REACTIONS:** Dermatitis and allied symptomatology have been reported.

If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

**DOSEAGE AND ADMINISTRATION:** Apply directly to the affected area every 2 hours or more often, as the severity of the infection and the degree of response indicate. Severe or stubborn ocular infections may require treatment for many days, and may also require oral therapy. Mild infections may respond within 48 hours.

**HOW SUPPLIED:** ACHROMYCIN tetracycline HCl Ophthalmic Ointment, USP, 1%:

NDC 0005-3501-51—18 oz tube

Store at Controlled Room Temperature 15°-30°C (59°-86°F).

**Reference:** 1. American Academy of Pediatrics: Prophylaxis and Treatment of Neonatal Gonococcal Infections, *Pediatrics*, 65:1047, 1980.

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American Cyanamid Company, Pearl River, N.Y. 10965

Rev. 8/86

12157

## ACHROMYCIN® Tetracycline Hydrochloride

Ophthalmic Suspension, USP, 1% Sterile

**DESCRIPTION:** ACHROMYCIN contains 10 mg of tetracycline hydrochloride per mL with Plastibase 50W and Light Mineral Oil as inactive ingredients.

Chemically, ACHROMYCIN is: [4S-(4a,4aa,5aa,6b,12aa)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride.

**INDICATIONS:** For the treatment of superficial ocular infections susceptible to ACHROMYCIN.

For prophylaxis of ophthalmia neonatorum due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. The Centers for Disease Control (U.S.P.H.S.) and the Committee on Drugs, the Committee on Fetus and Newborn, and the Committee on Infectious Diseases of the American Academy of Pediatrics recommend 1 percent silver nitrate solution in single-dose ampoules or single-use tubes of an ophthalmic ointment containing 0.5 percent erythromycin or 1 percent tetracycline as "effective and acceptable regimens for prophylaxis of gonococcal ophthalmia neonatorum."<sup>1</sup> (For infants born to mothers with clinically apparent gonorrhea, intravenous or intramuscular injections of aqueous crystalline penicillin G should be given: a single dose of 50,000 units for term infants or 20,000 units for infants of low birth weight. Topical prophylaxis alone is inadequate for these infants.)

The following organisms have demonstrated susceptibility to ACHROMYCIN:

<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
<i>Streptococci</i> including	<i>Neisseria species</i>
<i>Streptococcus pneumoniae</i>	<i>Chlamydia trachomatis</i>

When treating trachoma, a concomitant oral tetracycline is helpful.

Other organisms, not known to cause superficial eye infections, but with demonstrated susceptibility to ACHROMYCIN, have been omitted from the above list.

ACHROMYCIN does not provide adequate coverage against:

<i>Haemophilus influenzae</i>	<i>Pseudomonas aeruginosa</i>
<i>Klebsiella/Enterobacter species</i>	<i>Serratia marcescens</i>

**CONTRAINDICATIONS:** This product is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

**PRECAUTIONS:** The use of antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections appear during therapy, appropriate measures should be taken.

**ADVERSE REACTIONS:** Dermatitis and allied symptomatology have been reported.

If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

**DOSEAGE AND ADMINISTRATION:** For most susceptible bacterial infections shake well, then gently squeeze the plastic dropper bottle to instill 2 drops in the affected eye, or if necessary, in both eyes, 2 or 4 times daily, or more frequently, depending upon the severity of the infection. Very severe infections may require days of treatment, whereas other cases may be cured by instillation with much less frequency for 48 hours.

In acute and chronic trachoma, instill 2 drops in each eye 2 to 4 times daily. This treatment should be continued for 1 to 2 months, except that certain individual or complicated cases may require a longer duration. A concomitant oral tetracycline is helpful.

For unit dose administration and convenience, the DISPENSER may be used. Immediately prior to use, simultaneously roll, invert and squeeze DISPENSER between thumb and fingers. Repeat several times to mix contents well. Use aseptic technique to cut the tip of the DISPENSER, thereby maintaining sterility. Discard first two drops before instilling drops in eye(s). Instill two drops in eye(s), then discard DISPENSER.

**HOW SUPPLIED:** ACHROMYCIN is supplied as follows:

NDC 0005-3505-18—4 mL plastic dropper type bottle

Store at Controlled Room Temperature 15°-30°C (59°-86°F).

**Reference:** 1. American Academy of Pediatrics: Prophylaxis and Treatment of Neonatal Gonococcal Infections, *Pediatrics*, 65:1047, 1980.

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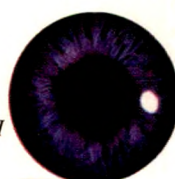
**CHLAMYDIA  
TRACHOMATIS**

**STAPHYLOCOCCUS  
AUREUS<sup>†</sup>**



**STREPTOCOCCI<sup>‡</sup>**

**ESCHERICHIA COLI**



**NEISSERIA  
GONORRHOEAE**

- ▼ Active against *N gonorrhoeae*, the principal cause of acute purulent conjunctivitis<sup>2,5</sup>
- ▼ Active against a wide range of gram-positive and gram-negative cocci and bacilli<sup>2,5,6</sup>
- ▼ Allergic reactions or irritation are rarely reported<sup>3§</sup>
- ▼ Available in both ointment and suspension
- ▼ Extensive clinical experience

\*Although a useful guide, *in vitro* data do not necessarily correlate with clinical results.

<sup>†</sup>Tetracycline is not the drug of choice for any type of staphylococcal infection.

<sup>‡</sup>Tetracycline is not the drug of choice for streptococcal infections.

<sup>§</sup>This product is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

Please see adjacent page for references and full Prescribing Information.

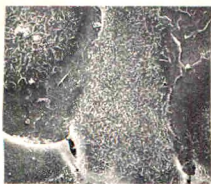
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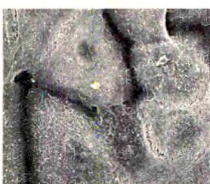
Scanning Electron Micrographs  
Of Human Corneal Epithelial Cells  
Treated With Ocular Lubricants  
For 60 Minutes (In Vitro-1000X  
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Significance Is Unknown)<sup>1</sup>



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Lubricant Ophthalmic Solution  
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**Tears Nature® II**  
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• Compressed anterior  
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• Some cytoplasmic pitting



**HypoTears®**  
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• Pitted cytoplasm  
• Slight cellular retraction  
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*An advanced formulation that may help maintain epithelial cell integrity. Celluvisc Solution provides patient comfort without compromising cell morphology; cell viability; or epithelial barrier function (in vitro data, clinical significance unknown).<sup>2</sup>*

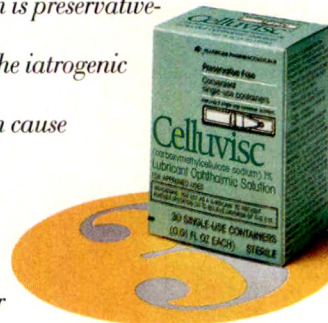
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*And, Celluvisc Solution is preservative-free, thus eliminating the iatrogenic effects preservatives can cause severe dry eye patients.*

*Celluvisc Solution.*

*The serious solution for*

*severe dry eye associated with ocular surface disease.*



# Celluvisc® Lubricant Ophthalmic Solution

*Contains no preservatives or EDTA.*

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WHEN SYMPTOMS ARE

# SEVERE

1. Data on file, Allergan, Inc. A collaborative study with M. Trousdale, Ph.D. et al at Estelle Doheny Eye Institute.

2. Adams, J.L., Wilcox M.J., Trousdale M.D. et al. Morphological and physiological effects of artificial tear formulations on corneal epithelial derived cells. Invest Ophthalmol Visual Sci 1989;30 (Suppl 3):523.

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## Fenestrated Sheen Macular Dystrophy

Scott R. Sneed, M.D., and Paul A. Sieving, M.D.

We examined a family with fenestrated sheen macular dystrophy. The red macular lesions were strikingly apparent in the propositus and more subtle in one affected cousin. Pronounced macular retinal pigment epithelial disruption or mottling was present in the father of the propositus, who also had markedly reduced electroretinogram rod and cone responses. The extent of electroretinogram amplitude reduction indicates abnormal function of the peripheral retina in addition to the clinically evident macular changes. Affected family members showed peripheral retinal pigment epithelial granularity. Central visual acuity remained normal despite the presence of macular lesions.

**F**ENESTRATED SHEEN MACULAR DYSTROPHY is a rare autosomal dominant macular dystrophy. Only three families with this entity have been previously described, two from the United States<sup>1,2</sup> and one from Norway.<sup>3</sup> This macular dystrophy is characterized in the early stages by small, red, demarcated lesions located in the deep neurosensory retina. These are apparent by color alone and do not have thickening or thinning of the retina, and consequently they have been termed fenestrations. Macular retinal pigment epithelial alterations have been described in patients 20 years of age and older. These changes appeared more noticeable in older individuals and were annular in appearance by the fourth decade. Affected patients in the three previously described pedigrees have shown little to no visual acuity deficit, even in middle age, despite fluorescein angiographic retinal pigment epithelial window defects in

older patients. At the 18-month follow-up examination, two patients showed evidence of progression, with enlargement of fenestrations in a 12-year-old patient and more extensive retinal pigment epithelial changes in a 56-year-old patient.<sup>4</sup>

We examined a family with fenestrated sheen macular dystrophy and studied the clinical and electrophysiologic findings.

### Material and Methods

Burian-Allan bipolar corneal electrodes were used with 0.5% proparacaine hydrochloride topical anesthesia to record electroretinograms after dilating pupils fully with 10% phenylephrine hydrochloride and 1% tropicamide. A 10-msec xenon flash was presented in a ganzfeld (full-field) bowl; stimulus intensities were calibrated with a photometer. Electroretinogram responses were amplified at 0.1 to 1,000 Hz ( $-3$  dB points) and digitized for display and storage.

Electroretinograms were recorded after one hour of dark adaptation, first with dim blue stimuli (440-nm peak, 70-nm half width,  $-1.86$  log cd-sec/m<sup>2</sup>) to elicit rod-predominant responses at two-second intervals. Next, white flashes (0.62 cd/m<sup>2</sup>) were used to elicit dark-adapted single responses that were approximately 75% from the rod and 25% from the cone system. After light adaptation at 40 log cd-sec/m<sup>2</sup> for five minutes in the ganzfeld bowl, single white flashes (1.0 log cd-sec/m<sup>2</sup>) were used to elicit cone-predominant responses. Population normal values were determined from 40 normal subjects, ranging in age from 5 to 60 years.

After dark adapting the patient for one hour, psychophysical final thresholds were measured in each eye separately. Test flashes of 0.8 second of a 5.7-degree target from a Goldmann-Weekers dark adaptometer were used to test fixation and points 20 degrees in the periphery of the superior, inferior, nasal, and temporal retina. Results were reported as log unit eleva-

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tion above normal rod final threshold determined from a population of 25 normal subjects.

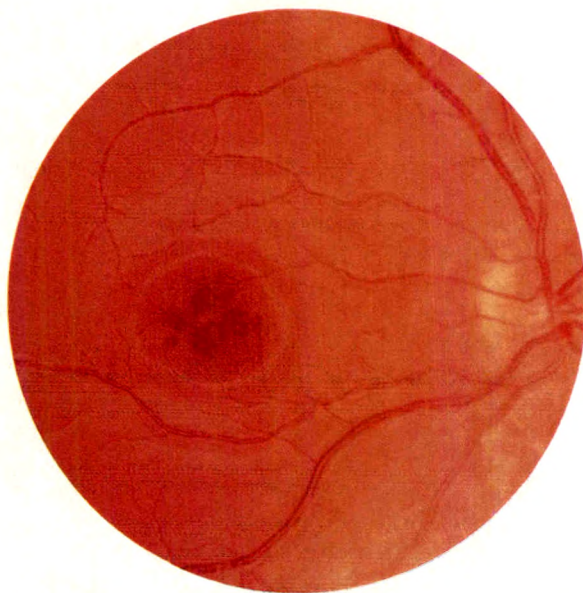
Subjects were tested by Ishihara plates under combined fluorescent and incandescent lighting and by Farnsworth D-15 panel under McBeth standard lighting.

### Case Reports

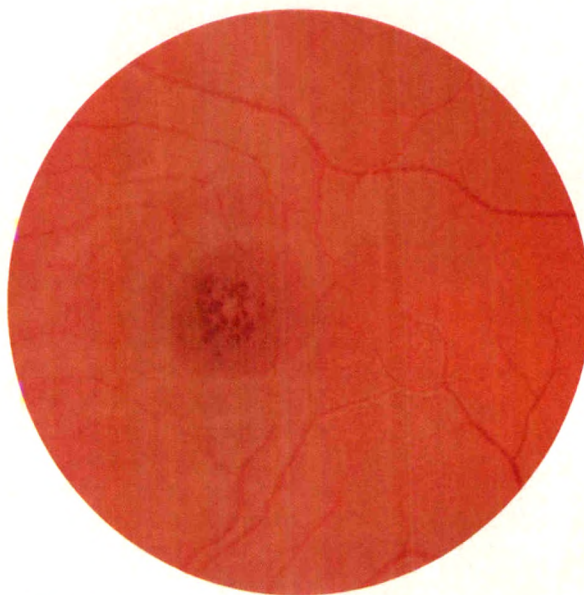
#### Case 1 (III-3)

The propositus, a 7-year-old white boy, was referred for red lesions in both maculae. He had been examined previously by other ophthalmologists and was believed possibly to have juvenile X-linked retinoschisis; however, an electroretinogram failed to confirm this.

On examination, visual acuity was R.E.: 20/20 and L.E.: 20/25 and J1+ bilaterally at near without correction. Results of the anterior segment examinations and intraocular pressure measurements were normal bilaterally. Ophthalmoscopic examination with a dilated pupil showed no vitreous cells, and the disk and retinal vessels were normal bilaterally. Irregular red lesions of variable size were present in both maculae and appeared to be at the level of the deep retina (Figs. 1 and 2). These red lesions were best seen with slightly indirect



**Fig. 1** (Sneed and Sieving). Case 1, propositus (III-3). The right eye demonstrating the deep retinal red figures in the central macula.



**Fig. 2** (Sneed and Sieving). Case 1, propositus (III-3). The left eye demonstrating the deep retinal red figures in the central macula.

lighting, and the overlying internal limiting membrane was smooth. No thickening or thinning of the retina was evident. The peripheral retinal pigment epithelium showed pigment disruption and mottling.

Results of fluorescein angiography of both eyes were normal and showed no evidence of retinal pigment epithelial disruption in the central macula (Figs. 3 and 4). The macular lesions were not visible at any stage of the fluorescein angiogram. Peripheral visual fields were tested on a Goldmann perimeter with V<sub>4e</sub> and I<sub>4e</sub> white targets and showed full isopters and no scotomata in both eyes. The patient identified correctly all Ishihara color plates with each eye. The Farnsworth D-15 color panel showed two crossing errors in the right eye (normal limit for a young child) and no crossing errors in the left eye (normal result). Dark-adapted rod final thresholds were normal in both eyes. The electroretinograms showed borderline low-normal cone and rod amplitudes, and cone 30-Hz flicker response timing was normal bilaterally.

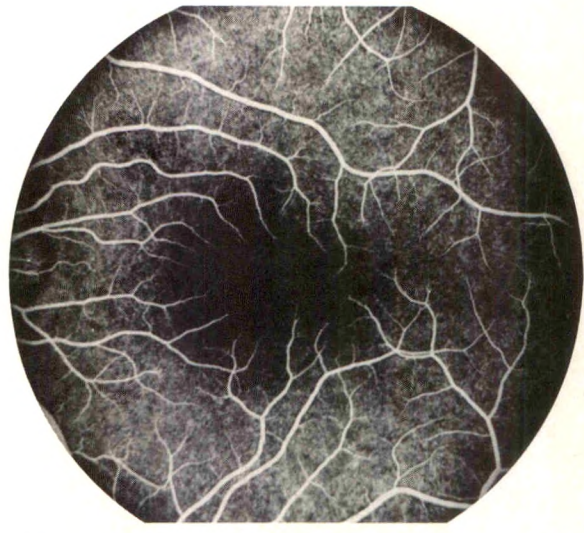
#### Case 2 (II-3)

The 29-year-old father was visually asymptomatic. Visual acuity was 20/20 in both eyes without correction. Results of anterior segment examinations and intraocular pressure meas-





**Fig. 3** (Sneed and Sieving). Case 1, propositus (III-3). Normal fluorescein angiogram of the right eye.

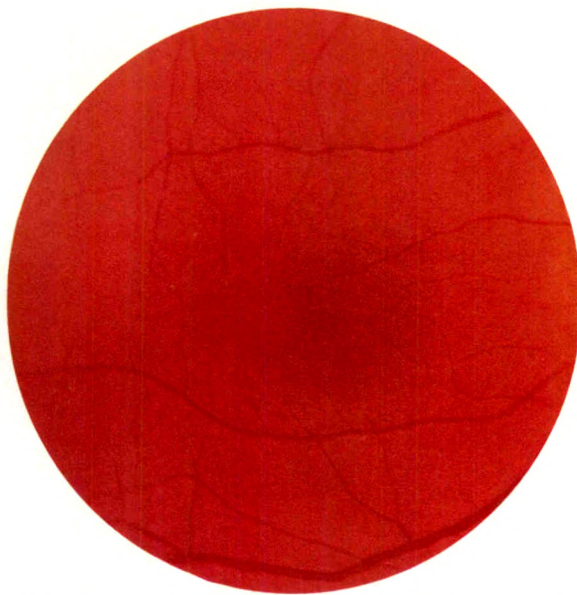


**Fig. 4** (Sneed and Sieving). Case 1, propositus (III-3). Normal fluorescein angiogram of the left eye.

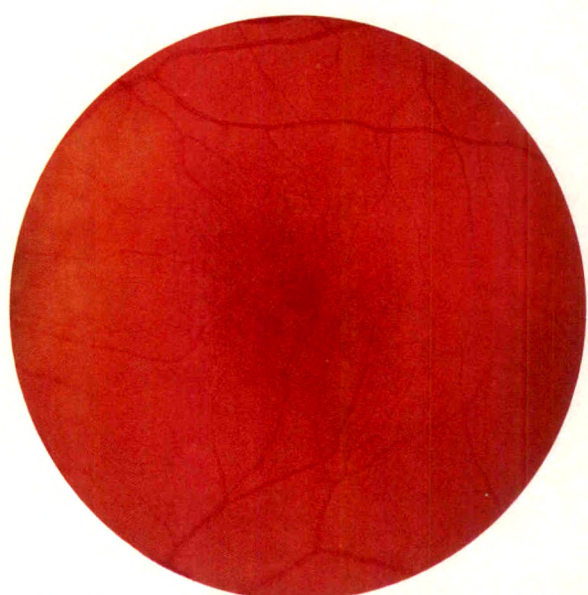
urements were normal bilaterally. Ophthalmoscopic examination with a dilated pupil showed normal optic disks and vessels. There were no vitreous cells. Heavy retinal pigment epithelial granularity was present in both maculae in an annular configuration; however, there was no evidence of red spots in either eye (Figs. 5 and

6). There was markedly abnormal retinal pigment epithelial granularity throughout the periphery, with areas of depigmented retinal pigment epithelium nasally.

Fluorescein angiography demonstrated diffuse hyperfluorescent abnormalities at the level of the retinal pigment epithelium in the macula

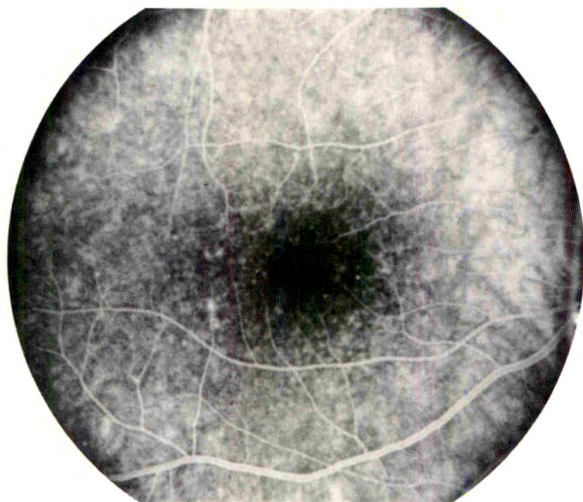


**Fig. 5** (Sneed and Sieving). Case 2, father (II-3). The right eye demonstrating the retinal pigment epithelial mottling in the macula.

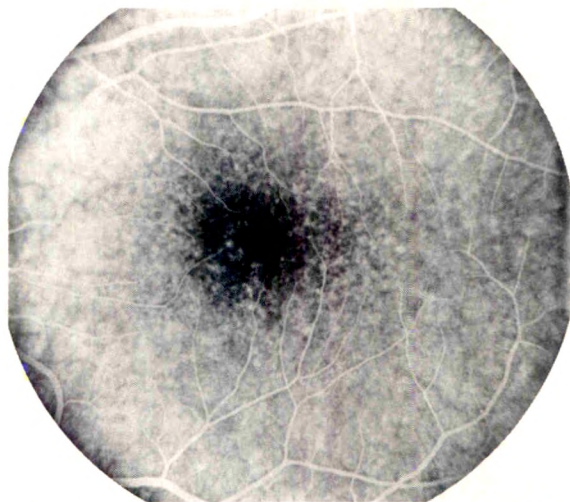


**Fig. 6** (Sneed and Sieving). Case 2, father (II-3). The left eye showing the retinal pigment epithelial mottling in the macula.





**Fig. 7** (Sneed and Sieving). Case 2, father (II-3). Fluorescein angiogram of the right eye demonstrating the retinal pigment epithelial alterations and window defects.



**Fig. 8** (Sneed and Sieving). Case 2, father (II-3). Fluorescein angiogram of the left eye demonstrating retinal pigment epithelial alterations and window defects.

of both eyes (Figs. 7 and 8), consistent with window defects and without evidence of leakage. Color vision was normal by Ishihara plates and Farnsworth D-15 testing. Dark-adapted final thresholds were normal in the superior, inferior, nasal, and temporal periphery at 20 degrees but were elevated by 0.4 log units at fixation (abnormal). Peripheral visual fields by Goldmann perimetry were normal to  $V_{4e}$  but were constricted by approximately 10 degrees from normal to the  $I_{4e}$  target. The rod b-wave electroretinogram was reduced by more than 50% from the low limit of normal. Cone flicker responses also were reduced by 50% from the low limit of normal, and the implicit time was delayed (37 msec; normal, approximately 32 msec). Cone light-adapted b-wave electroretinogram to single white flash was also abnormally reduced.

#### Case 3 (III-1)

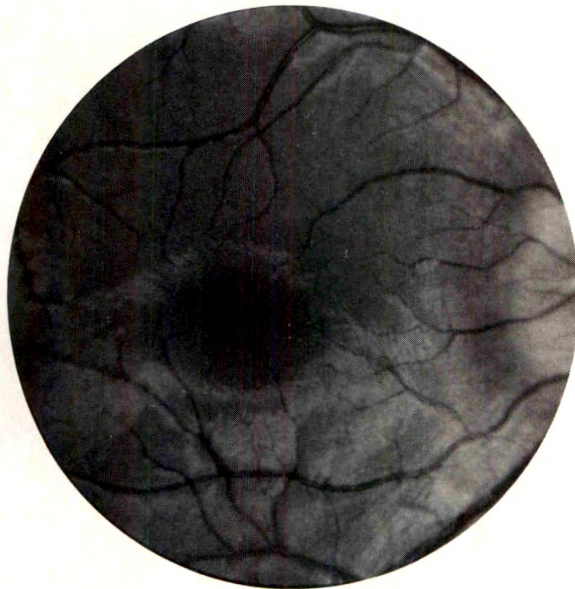
A cousin of the proband, a 7-year-old boy, was visually asymptomatic. Best-corrected visual acuity was 20/50 bilaterally. Results of anterior segment examinations and intraocular pressure measurements were normal. Ophthalmoscopy showed a blonde periphery with normal stippling of the retinal pigment epithelium. There was abnormal granularity of the retinal pigment epithelium in the macula bilaterally with definite but faint red spots in the outer

retina (Fig. 9). Both optic disks were swollen with no hemorrhage or subretinal fluid. The optic disk abnormalities had been documented the previous year. Results of a computed tomographic scan of the head and orbits were normal, and the disk changes were believed to be congenital. Fluorescein angiography showed no retinal pigment epithelial abnormalities. Ultrasound showed no evidence of optic disk drusen. Dark-adapted rod final thresholds were normal. Rod and cone electroretinogram responses were both reduced and were each only 60% of low-normal limits. The implicit time was normal. Color vision showed seven errors on Farnsworth D-15 testing along an acquired tritan axis for each eye.

#### Case 4 (III-2)

Another cousin of the proband, a 5-year-old boy, was visually asymptomatic. Visual acuity was 20/30 bilaterally. Results of anterior segment examinations and intraocular pressure measurements were normal. The peripheral fundus was blonde. A mild granularity of the retinal pigment epithelium was present in the macula with an apparent sheen overlying the macula. We judged this to be within the spectrum of normal at this time. No red spots were seen. Color vision was normal. Dark adaptation and electrophysiologic testing were not performed.





**Fig. 9** (Sneed and Sieving). Case 3, cousin (III-1). The right eye demonstrating less distinct red figures in the central macula and the associated anomalously elevated optic disk.

#### **Case 5 (II-4)**

The 29-year-old mother was visually asymptomatic. Best-corrected visual acuity was R.E.: 20/20 and L.E.: 20/15. Results of anterior segment examinations and intraocular pressure measurements were normal. Retinal examination showed a blonde but normal fundus. All Ishihara color plates were identified correctly, and no errors were noted on Farnsworth D-15 testing. Goldmann perimetry showed normal  $V_{4e}$  and  $I_{4e}$  isopters for each eye.

#### **Case 6 (II-2)**

The 31-year-old uncle was visually asymptomatic. Visual acuity was 20/20 bilaterally. Results of anterior segment examinations and intraocular pressure measurements were normal. Ophthalmoscopic examination with a dilated pupil showed a blonde periphery with normal stippling of the retinal pigment epithelium. There was mild granularity of the retinal pigment epithelium in the macula but no red dots.

Results of fluorescein angiography were normal. Color vision was normal in the left eye and borderline normal in the right eye. Dark adaptation was normal bilaterally. Electroretinogram responses were normal for both eyes.

#### **Case 7 (I-1)**

The 56-year-old paternal grandfather was visually asymptomatic. Visual acuity was 20/20 bilaterally. Results of anterior segment examinations and intraocular pressure measurements were normal. Ophthalmoscopic examination with a dilated pupil showed a normal retinal pigment epithelial granularity in the macula and periphery. Color vision was normal for the right eye, but the patient made four errors along an acquired tritan axis on Farnsworth D-15 testing of the left eye. Dark-adapted thresholds and electroretinograms were normal.

#### **Case 8 (I-2)**

The 53-year-old paternal grandmother had undergone extraocular muscle surgery at age 3 years for strabismus and had amblyopia in the right eye. Best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/25. Results of anterior segment examinations and intraocular pressure measurements were normal. The retina and retinal pigment epithelium appeared normal in both eyes.

#### **Case 9 (III-4)**

The 4-year-old sister was visually asymptomatic. Results of visual acuity testing, slit-lamp biomicroscopy, and ophthalmoscopic examination with a dilated pupil were normal in both eyes.

### **Discussion**

This family is only the fourth pedigree described with fenestrated sheen macular dystrophy (Fig. 10). The characteristic red lesions in the deep retina of the proband are identical to the previously published color photographs and paintings.<sup>1,3</sup> The retinal pigment epithelial mottling in an annular configuration in the father of the proband also coincides with the previously described pedigrees. Good visual acuity was documented in the present pedigree, except for the 7-year-old cousin (Case 3, III-1). The reduced visual acuity in this patient was believed to be caused by the anomalous disks. The presence of anomalous optic disks may simply be coincidental. Abnormal retinal pigment epithelial mottling in the macula and



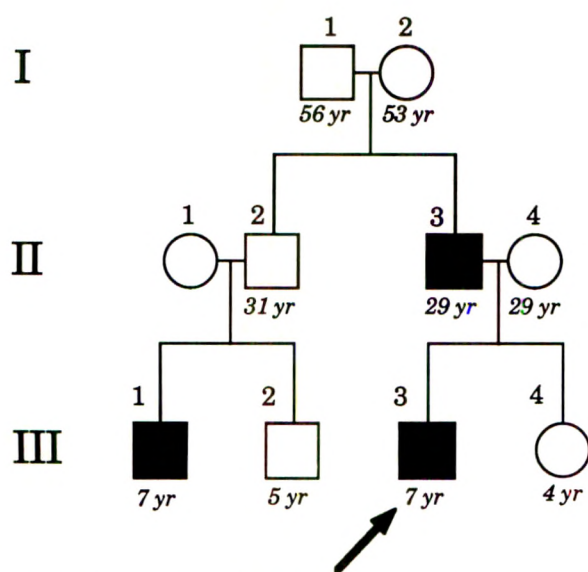


Fig. 10 (Sneed and Sieving). Family pedigree. Open square or circle indicates normal; solid square indicates affected; and arrow indicates the proband.

periphery was present in all three affected members of this pedigree.

Although we did not find clear fundus or macular changes in three consecutive generations, the inheritance pattern in our family is consistent with autosomal dominant transmission with reduced penetrance. Only the first pedigree described<sup>1</sup> showed three generations affected, whereas the subsequent two families, like ours, had fewer than three generations affected.<sup>2,3</sup>

Two of our family members (Case 2, II-3, and Case 3, III-1) had abnormally reduced rod and cone electroretinogram amplitudes. O'Donnell and Welch<sup>1</sup> initially reported reduced photopic but not scotopic electroretinograms in their patients, but repeat examination showed normal electroretinogram amplitudes in all of their patients.<sup>4</sup> Our finding of markedly reduced rod and cone electroretinograms indicates abnormal retinal function geographically more widespread than indicated by the macular lesions alone.

The small red macular fenestrations seen in younger individuals appear similar to the macular lesions described in acute macular neuroretinopathy. Patients with acute macular neuroretinopathy, however, are generally symptomatic and have decreased vision with or without paracentral scotomata in one or both

eyes.<sup>5</sup> Acute macular neuroretinopathy is often preceded by an influenzalike syndrome and also has been described after acute hypertension caused by intravenous sympathomimetics (epinephrine, ephedrine).<sup>6</sup> Although some patients with acute macular neuroretinopathy may have small red spots at the level of the outer retina, other patients have been described with larger, more geographic macular lesions.<sup>6</sup> Visual acuity usually improves, and the macular lesions and scotomata tend to resolve over a period of months in most patients with acute macular neuroretinopathy. No heritable cases of acute macular neuroretinopathy have been reported.

In comparison, patients with fenestrated sheen macular dystrophy are usually asymptomatic with good visual acuity. The macular red fenestrations show no tendency for acute resolution, and an earlier report described enlargement of a fenestration during a period of 18 months.<sup>4</sup> If the electroretinogram is reduced, as in our Cases 2 and 3, this may help distinguish fenestrated sheen macular dystrophy from acute macular neuroretinopathy.

Retinal pigment epithelial mottling occurs in the macula of older affected individuals with fenestrated sheen macular dystrophy as the red fenestrations gradually disappear. These retinal pigment epithelial alterations may be manifest as an annular maculopathy. Other causes of an annular maculopathy (chloroquine, rod-cone dystrophy, cone dystrophy, Stargardt's disease, and benign concentric annular dystrophy) should be considered when examining an older patient with fenestrated sheen macular dystrophy. Thorough examination of other family members with ophthalmoscopy, fluorescein angiography, and electrophysiologic testing should allow differentiation of the diseases causing an annular maculopathy.

Fenestrated sheen macular dystrophy is an infrequently reported, autosomal dominant macular dystrophy characterized by good visual acuity, despite small red macular fenestrations in younger patients and macular retinal pigment epithelial mottling in later stages of the disease. Patients tend to have good visual acuity even in later stages of the disease. Our findings of peripheral retinal pigment epithelial changes and, in some cases, reduced electroretinogram amplitudes suggest that fenestrated sheen macular dystrophy can involve the peripheral retina also. Longer follow-up will be



necessary to document whether there is possible disease progression in this interesting macular dystrophy.

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#### ACKNOWLEDGMENT

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#### OPHTHALMIC MINIATURE

Nor is my invisibility exactly a matter of biochemical accident to my epidermis. That invisibility to which I refer occurs because of a peculiar disposition of the eyes of those with whom I come in contact. A matter of the construction of their *inner* eyes, those eyes with which they look through their physical eyes upon reality. I am not complaining, nor am I protesting either. It is sometimes advantageous to be unseen, although it is most often rather wearing on the nerves. Then too, you're constantly being bumped against by those of poor vision. Or again, you often doubt if you really exist.

Ralph Ellison, *Invisible Man*  
New York, Vintage Books, 1972



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# Symptomatic Retinoschisis-Detachment Involving the Macula

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and Froncie A. Gutman, M.D.

We treated three patients (four eyes) in whom posteriorly situated retinoschisis-detachments became symptomatic because of elevation of a limited area of full-thickness retina at the macula adjacent to these lesions. Laser photocoagulation alone was successful in achieving long-term macular reattachment in one eye but failed in both eyes of a bilaterally affected patient. In this patient, retinal cryopexy, external drainage of subretinal and retinoschisis cavity fluid, and intravitreal air injection attained long-term macular reattachment and retinoschisis cavity collapse in both eyes. In the third patient, cryopexy, drainage of subretinal and retinoschisis cavity fluid, and scleral buckling failed to reattach the retina. Subsequent laser photocoagulation induced reabsorption of subretinal fluid but without retinoschisis cavity collapse. Alternative management strategies for these unusual cases include retinal cryopexy alone and vitrectomy techniques.

**D**EGENERATIVE RETINOSCHISIS is a common condition of the peripheral retina<sup>1-3</sup> and is almost always asymptomatic.<sup>4,7</sup> When outer layer breaks are present, retinoschisis is occasionally complicated by localized detachment of the outer retinal layer. Byer<sup>4</sup> defined this as schisis-detachment,<sup>4</sup> and we have used this term in our previous work.<sup>8,9</sup> The term, however, is not accurate. We therefore propose that the term retinoschisis-detachment, which was used in a

section heading by Byer,<sup>4</sup> be used for these lesions.

In retinoschisis-detachments, the outer layer detachment is usually confined to the area of the retinoschisis. The detachment is almost always asymptomatic, infrequently progressive, and rarely requires treatment. This contrasts with progressive, symptomatic rhegmatogenous retinal detachment, which occasionally complicates degenerative retinoschisis and is almost the only complication of retinoschisis in which intervention is required.<sup>1,4,10</sup> We treated a rare complication of retinoschisis-detachment in four eyes of three patients. In these four eyes, posteriorly situated retinoschisis-detachments became symptomatic because of posterior extension of the fluid under the outer layer to involve the maculae. A combination of laser photocoagulation and surgery was performed in three of the eyes and laser photocoagulation only in the fourth eye. We also studied the long-term outcome. One of these patients has been briefly described elsewhere.<sup>11</sup>

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## Case Reports

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### Case 1

On Sept. 29, 1980, a 58-year-old man was examined for a 30-year history of an intermittent superior paracentral visual field defect in his right eye, which had been constant for the previous three weeks. Except for mild myopia, his ocular history was unremarkable. Best-corrected visual acuity was R.E.: 20/25 and L.E.: 20/20. In the right eye, a two-clock hour area of retinoschisis was located superiorly in which were two medium-sized outer layer breaks but no inner layer breaks or outer layer elevation. There was also a large area of retinoschisis inferotemporally from the 5:30 to 10:00 o'clock meridians, which extended posteriorly to the inferotemporal arcade. This area contained

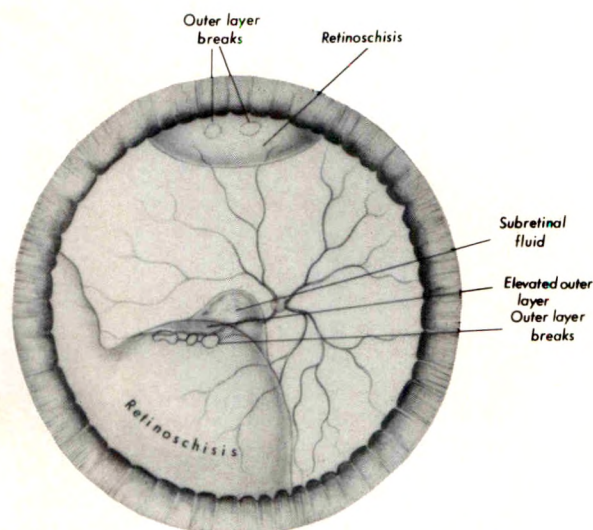
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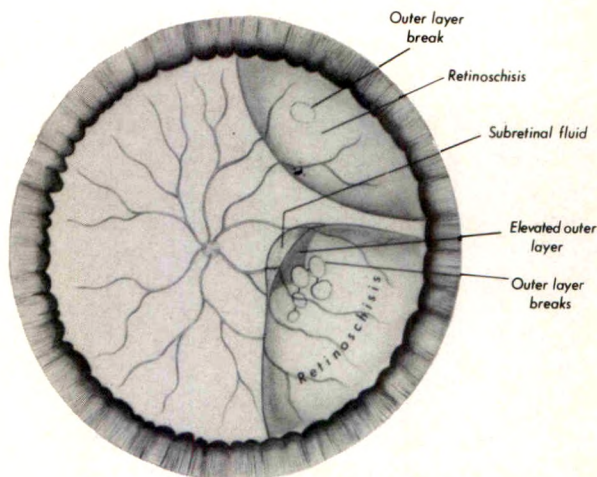


**Fig. 1** (Ambler, Gass, and Gutman). Case 1, right eye. Large inferotemporal area of retinoschisis with three posterior outer layer holes, two of which have elevated posterior margins. Extending superiorly from the holes is a shallow detachment of the outer retinal layer and adjacent full-thickness retina, including the macula. Visual acuity is 20/25.

three medium-sized posterior outer layer breaks. The two most posterior of these breaks, which straddled the inferior arcade vessels, had elevated posterior margins. Extending superiorly from these holes was a shallow detachment of the outer retinal layer and adjacent full-thickness retina, including the macula (Fig. 1). No inner layer breaks were detected.

In the left eye, there were two large retinoschisis cavities in the temporal retina. The superior cavity had one outer layer break but no outer layer elevation. The inferior retinoschisis had five posterior medium-sized outer layer breaks. There were no inner layer breaks. In the inferior retinoschisis cavity, the posterior edge of the most posterior outer layer hole was elevated and communicated posteriorly with an area of detached outer layer. Posterior to this was a small area of full-thickness retinal detachment. The posterior margin of this full-thickness detachment was 2 disk diameters from the fovea (Fig. 2). A diagnosis of bilateral retinoschisis-detachment was made.

Argon laser photocoagulation was performed in the left eye to surround the area of elevated outer layer and the five adjacent outer layer breaks. One week later, laser photocoagulation was also performed in the right eye to surround the posterior outer layer holes in an attempt to



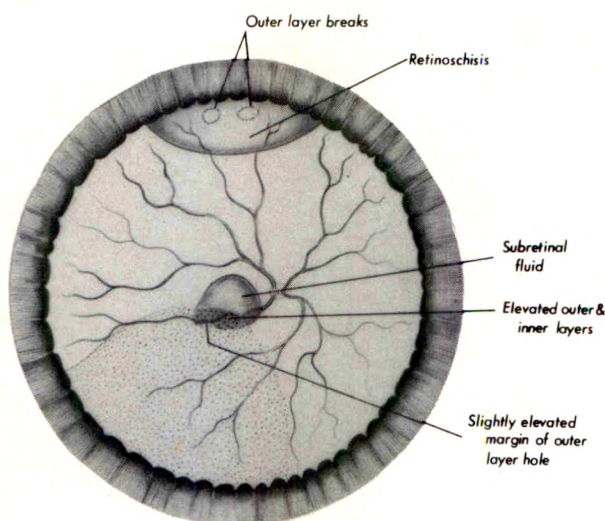
**Fig. 2** (Ambler, Gass, and Gutman). Case 1, left eye. Two large retinoschisis cavities. The inferior cavity has five posterior outer layer breaks, the most posterior of which has an elevated posterior edge. This communicates with an area of elevated outer layer and adjacent full-thickness retinal detachment.

flatten the outer layer. In both eyes, the laser treatments were of fairly light intensity and limited area. Follow-up during a six-month period demonstrated that the laser therapy had failed to flatten the outer layer in the right eye. In this eye, the macula remained detached, and best-corrected visual acuity had decreased to 20/50.

Because of the decrease in visual acuity in the right eye, surgical intervention was undertaken. Retinal cryopexy (double-freeze technique) was applied to the entire area of inferior retinoschisis in an attempt to obtain permanent collapse of the retinoschisis. This was followed by external drainage of the retinoschisis cavity fluid and intraocular gas injection. At the end of this procedure the retinoschisis cavity was completely collapsed. The patient was positioned prone after the procedure. Subretinal fluid, however, persisted in the macular area and was still present three weeks later (Fig. 3). Laser photocoagulation was then applied to a slightly elevated outer layer break, which was communicating with the fluid. The fluid slowly reabsorbed until the retina was totally flat one year after the surgical procedure. Visual acuity improved to 20/30 during the next year. There was slight preretinal macular fibrosis.

At a follow-up examination on Nov. 21, 1983, the outer layer retinal breaks in the inferior retinoschisis cavity of the left eye had progressively become elevated during 2½ years. The previously localized subretinal fluid had slowly





**Fig. 3** (Ambler, Gass, and Gutman). Case 1, right eye. Three weeks after retinal cryopexy, drainage of retinoschisis cavity fluid, and gas injection, a small amount of subretinal fluid persists at the macula. This communicates with the slightly elevated posterior margin of an outer layer break. Retinal cryopexy is present inferiorly.

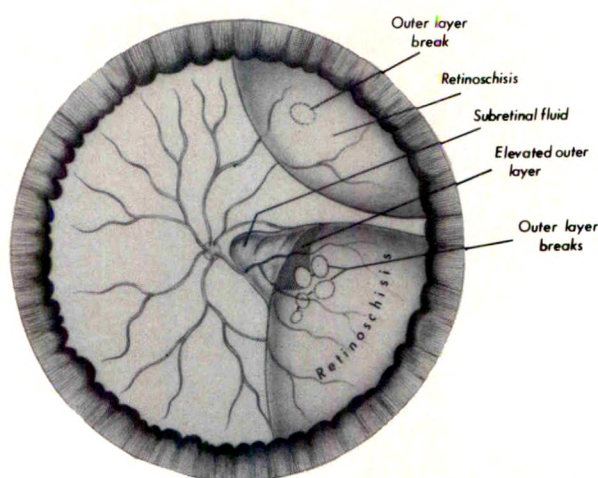
extended posteriorly through the narrow band of noncontiguous laser scars to involve a larger area of full-thickness retina, including the fovea (Fig. 4). Visual acuity remained 20/25. One day before surgery, all outer layer breaks were again surrounded with laser photocoagulation. At surgery, cryopexy was performed to the entire area of both retinoschisis cavities, and the two retinoschisis cavities were drained via separate sclerotomies. Intraocular air injection was then performed. Postoperatively the patient was positioned prone.

On the first postoperative day, there was persistence of subretinal fluid in the macular area but complete collapse of the retinoschisis cavity. This fluid at the macula did not totally reabsorb until nine months after surgery, at which time visual acuity was 20/30.

At the most recent follow-up examination, four years after the last procedure, best-corrected visual acuity was R.E.: 20/50 and L.E.: 20/30. There was no retinal detachment, and the retinoschisis cavities remained totally collapsed. Mild preretinal macular fibrosis was present in both eyes, and there were large areas of chorioretinal scarring in the previous areas of retinoschisis.

#### Case 2

A 60-year-old woman had a recent decrease in vision in her left eye. Best-corrected visual



**Fig. 4** (Ambler, Gass, and Gutman). Case 1, left eye. After 2½ years of follow-up, the localized subretinal fluid posterior to the retinoschisis cavity has extended posteriorly to involve a larger area of full-thickness retina, including the macula. Visual acuity is 20/25.

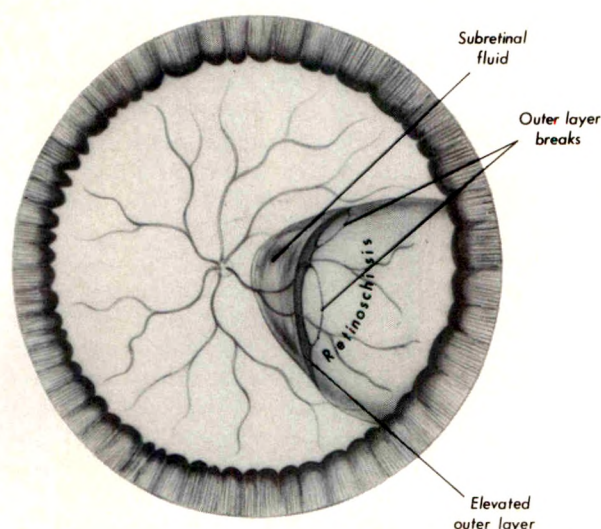
acuity was R.E.: 20/20 and L.E.: 20/50. In the left eye, a temporal area of bullous retinoschisis extended from the 2:30 to the 5:00 o'clock meridians. There were two large outer layer breaks adjacent to the posterior margin of the retinoschisis. The posterior edge of both of these breaks was elevated and communicated posteriorly with an area of full-thickness retinal detachment that involved the macula (Fig. 5). The right eye had an area of retinoschisis inferotemporally.

Retinal cryopexy was applied to the posterior aspect of the retinoschisis cavity, surrounding the outer layer breaks, and to the posterior margin of the area of retinoschisis. The entire retinoschisis cavity was not treated. Retinoschisis cavity fluid was then drained externally at the equator. A 4-mm radial sponge was then placed to include the outer layer breaks. The retinoschisis cavity was completely collapsed, but the subretinal fluid posterior to the retinoschisis was unchanged.

Two weeks later, part of the retinoschisis cavity had reformed, and subretinal fluid persisted behind the retinoschisis cavity and still involved the macula. Argon laser photocoagulation was applied to the posterior edge of the outer layer breaks and to the elevated full-thickness retina just posterior to the retinoschisis cavity (Fig. 6).

During the next 12 months, the subretinal fluid gradually reabsorbed, and visual acuity improved to 20/30. At the most recent follow-





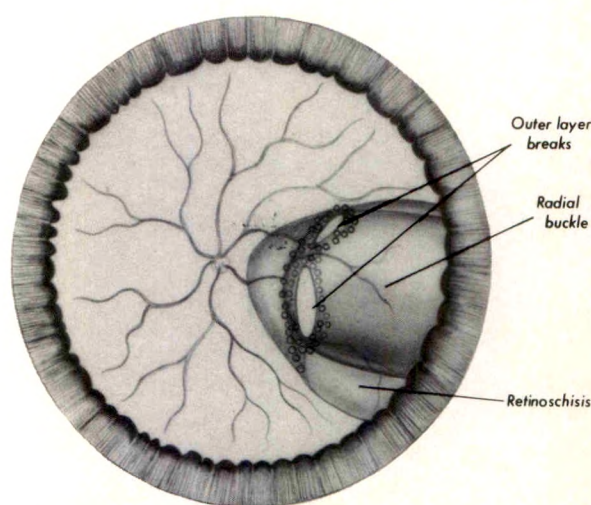
**Fig. 5** (Ambler, Gass, and Gutman). Case 2. Temporal area of bullous retinoschisis with two large outer layer breaks adjacent to its posterior margin. The posterior edge of both these breaks is elevated and communicates posteriorly with an area of full-thickness retinal detachment that involves the macula. Visual acuity is 20/50.

up examination, 11 years after the surgical intervention, best-corrected visual acuity was 20/50. The retina posterior to the retinoschisis cavity was flat with mild retinal pigment epithelial changes at the macula. The anterior half of the retinoschisis cavity persisted overlying the radial buckle. The area of retinoschisis in the right eye was unchanged.

### Case 3

A 66-year-old man was examined at the Bascom Palmer Eye Institute in April 1985 for a one-year history of metamorphopsia and progressive visual blurring in his right eye. Best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/20. He had a 3½-clock hour area of bullous retinoschisis temporally from the 7:00 o'clock to the 10:30 o'clock meridians in which were two large posterior outer layer breaks. The posterior edges of these breaks were elevated, and they communicated posteriorly with an area of shallow full-thickness retinal elevation that involved the macula (Fig. 7). The left eye had a superotemporal area of retinoschisis but no outer layer breaks. Because of current serious medical problems, treatment was deferred.

The patient returned to see one of us (J.D.M.G.) four months later. Visual acuity and fundus appearances were unchanged. Argon laser photocoagulation was applied around the



**Fig. 6** (Ambler, Gass, and Gutman). Case 2. Two weeks after scleral buckling and retinoschisis cavity drainage, the retinoschisis cavity has reformed. Subretinal fluid persists behind the retinoschisis cavity and still involves the macula. Photocoagulation burns surround the outer layer breaks.

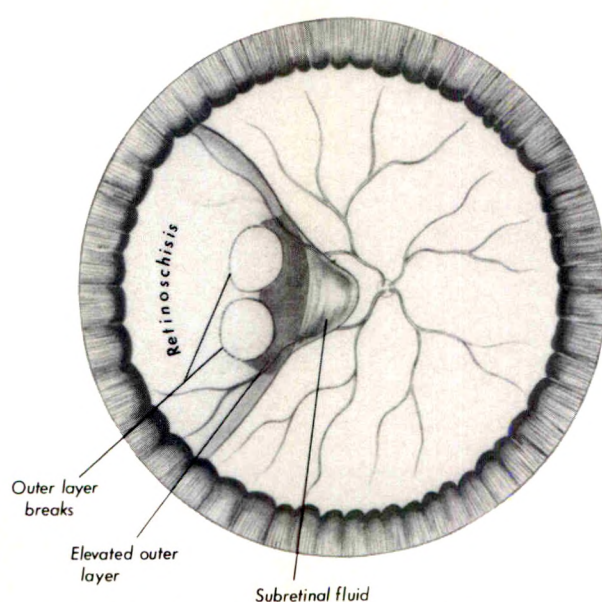
outer layer breaks and along the posterior margin of the retinoschisis in an attempt to isolate the retinal detachment in the macula from the retinoschisis cavity. The laser burns achieved in the areas of slight retinal elevation were of less intensity than in the areas of nondetachment around the holes.

Five months later, visual acuity in the right eye was 20/40. There was still some elevation of the retina around the posterior border of the holes and persistent retinal detachment in the macula. The retinoschisis cavity was unchanged. To achieve a zippering effect (that is, progressive flattening from less elevated to more elevated areas), several rows of moderately intense argon laser were added to the area of persistent retinal elevation at the edge of the holes and at the posterior margin of the retinoschisis. Seven months later, the subretinal fluid had reabsorbed and the outer layer breaks were sealed by chorioretinal adhesions. Best-corrected visual acuity was 20/30. In February 1989, 2½ years later, the findings were unchanged.

### Discussion

Degenerative retinoschisis is usually a disease of the peripheral retina and when uncomplicated by other abnormalities is almost always asymptomatic.<sup>4-7</sup> It is rare for retinoschisis





**Fig. 7** (Ambler, Gass, and Gutman). Case 3. Temporal area of bullous retinoschisis with two large posterior outer layer breaks. The posterior edges of the breaks are elevated and communicate posteriorly with an area of elevated outer layer and shallow full-thickness retinal detachment that involves the macula. Visual acuity is 20/70.

to extend to the temporal arcade vessels.<sup>4</sup> Even more rarely does the retinoschisis actually progress to involve the macula.<sup>4,5,10-15</sup> Even when complicated by retinoschisis-detachment (that is, elevation of the outer retinal layer associated with an outer layer break that remains substantially localized to the area of the retinoschisis), the condition is almost always asymptomatic.<sup>3,4</sup> Degenerative retinoschisis may become symptomatic for several reasons. Symptoms may occur because of the large area of absolute scotoma caused by the retinoschisis, particularly if it extends well posteriorly toward the macula. They can also occur in vitreous hemorrhage<sup>16,17</sup> or progressive full-thickness retinal detachment occurring in some patients with outer layer breaks.<sup>8,12,18,19</sup> Because retinoschisis causes an absolute scotoma, elevation of the outer retinal layer confined to the area of the retinoschisis (retinoschisis-detachment) will generate no additional symptoms than those caused by the retinoschisis itself.

Except in the situation of progressive rhegmatogenous retinal detachment complicating retinoschisis, which occurs occasionally in those cases with outer layer breaks, even if a small amount of full-thickness retina adjacent to the retinoschisis cavity becomes elevated,

symptoms rarely occur since this full-thickness retinal detachment is usually peripheral and nonprogressive. In the four eyes of our patients, however, because of the posterior location of the retinoschisis-detachment, elevation of a small area of full-thickness retina adjacent to the retinoschisis-detachment caused symptoms because the macula was involved.

Three similar cases have been reported.<sup>12,19,20</sup> All were unilateral, and two were associated with giant outer layer breaks. One case progressed noticeably during a period of four weeks and was managed with vitrectomy, air-fluid exchange, and face-down positioning.<sup>12</sup> Although the retina remained attached six months postoperatively, bullous retinoschisis persisted. In the second case, clinical details were not reported, and this may have been a rapidly progressive and extensive retinal detachment complicating degenerative retinoschisis.<sup>20</sup> In this case, vitrectomy and air-fluid exchange were performed, but it is not clear from the report whether the retinoschisis cavity was drained internally or externally. Long-term follow-up was not reported in either of these two cases. Sneed and associates<sup>19</sup> described 12 patients in whom retinoschisis and retinal detachment were present. One of the two cases they described in detail may be similar to our cases. In this case, a single attempt at laser photocoagulation failed to achieve retinal reattachment after six weeks. The retina was reattached with vitrectomy, inner layer retinotomy, internal drainage of retinoschisis cavity and subretinal fluid, fluid-gas exchange, and endolaser photocoagulation. Cataract surgery was required 18 months later.

In 85 eyes treated and 49 patients followed up for retinoschisis, Okun and Cibis<sup>21</sup> reported that in eight eyes, spread of retinoschisis occurred posteriorly to the point of macular involvement. No further details were given, but we believe that these cases may have been similar to ours, that is, retinoschisis-detachments involving the macula rather than actual macular involvement by the retinoschisis. One of us (J.D.M.G.) has reported a case in which the actual retinoschisis cavity spread to the edge of the foveal pit.<sup>11</sup>

We believe that it is appropriate to classify the abnormality in our patients as symptomatic retinoschisis-detachment, not a retinal detachment complicating degenerative retinoschisis. We believe that this differentiation is not merely a semantic one but has significance for prognosis and the need for intervention. Retinal detachments complicating degenerative reti-



noschisis usually have progressed or will progress relatively rapidly to extensive retinal detachment and therefore almost always need surgical intervention. Retinoschisis-detachments, however, are usually localized, nonprogressive, and not sight-threatening and rarely require intervention. Byer<sup>4</sup> found that 11 of 13 retinoschisis-detachments, which he followed up for an average of 6.3 years, were entirely unchanged. In one case the height and extent of the lesion decreased with time and another decreased in height after cataract surgery, only to resume its previous size with further follow-up. He concluded that prophylactic treatment of retinoschisis-detachment is not indicated unless it becomes symptomatic or extensive.

We classified the abnormality in our patients as retinoschisis-detachment for several reasons. Subretinal fluid remained confined to a small area contiguous with outer layer breaks and did not extend far posterior to the posterior margin of the retinoschisis. Also, the detachment always remained shallow and progressed in area extremely slowly, always remaining confined to a relatively small area. The only reason that these retinoschisis-detachments became symptomatic was their location, which was close to the macula. Had these lesions been peripheral, they would have been asymptomatic and required no intervention.

Unfortunately, the best method of treatment of retinoschisis-detachment in those few cases where it is indicated is unclear. Laser photocoagulation applied around the outer layer breaks in the right eye of our bilateral case (Case 1) failed to flatten the outer layer and stop progression of the retinoschisis-detachment. This may have been because of the relatively light intensity of the laser burns. Had we elected to use repeated applications of more intense photocoagulation, we might have succeeded in isolating the retinoschisis-detachment from the macula as in Case 3, thereby allowing the macula to reattach.

Laser photocoagulation failed to wall off the retinoschisis-detachment in the left eye of Case 1, also possibly because of the light intensity used. Because of the course observed in the right eye, we operated on the left eye as soon as fluid progressed to involve the macula. The shorter period of macular involvement in the left eye may explain the better visual outcome when compared to the right eye.

In Case 3, despite elevation of the outer layer breaks, repeated laser photocoagulation alone succeeded in reattaching the retina. This appeared to occur in a zippering fashion; that is,

the retina progressively reattached from areas of less elevation to areas of greater elevation.

Retinal cryopexy, drainage of the retinoschisis cavity, and intravitreal air injection were eventually successful in both eyes of Case 1 in reattaching the retina and collapsing the retinoschisis cavity. Despite both eyes having collapsed retinoschisis cavities at the end of surgery, however, both eyes retained a small amount of subretinal fluid in the macular area. In both eyes this fluid took many months to reabsorb. Similarly in Case 2, reabsorption of the subretinal fluid took 12 months. Also in Case 3, no attempt was made to close the retinoschisis cavity with cryopexy. In view of the natural development of retinoschisis-detachment, we cannot be sure whether these maculae would have reattached spontaneously or whether the intervention was responsible for the outcome. We also do not know whether a different technique would have been better. In ten patients with retinoschisis-detachments, Cox and Gutow<sup>22</sup> reported a 100% success rate in reattaching the outer layer after retinal cryopexy alone. In all of their cases, however, detachment of the outer layer was confined to the area of retinoschisis. As previously stated, however, retinoschisis-detachment in the peripheral retina is benign and no intervention is required. Also, their technique included freezing a posterior rim of normal retina, which was not possible in any of the eyes in our series because of the foveal involvement.

Vitrectomy and intraocular gas injection is another possible management method. This could be performed with or without internal or external drainage of subretinal fluid. In two cases of retinal detachment complicating retinoschisis and one case similar to our bilateral case, Sulonen and associates<sup>12</sup> performed vitrectomy and air-fluid exchange followed by postoperative face-down positioning. Although the outer layer was reattached in all cases, the retinoschisis cavity did not remain collapsed in two of these cases. Also, one of their patients had a poor visual outcome because of proliferative vitreoretinopathy.

Escoffery and associates<sup>20</sup> also reported the use of vitrectomy and intraocular gas in three cases, one of which may be similar to our cases, but the clinical details of their cases were not reported. Scleral buckling was certainly contraindicated in three of the eyes in our series because of the posterior position in which the buckle would have to be placed.

The best form of management for the rare condition of symptomatic retinoschisis-detach-



ment involving the macula remains unclear. Because of the shallowness of the retinal detachment in the areas of retinoschisis in these cases, however, we recommend the following approach. Initial treatment should be moderately intense laser photocoagulation placed around the elevated outer layer break or breaks as well as along the posterior border of the retinoschisis cavity posterior to the equator, including the communication between the full-thickness retinal detachment and the retinoschisis cavity. Treatment in this area of communication offers the potential for preventing posterior extension of the retinoschisis as well as providing a second potential site for isolating the macula from the outer layer retinal holes. To achieve a zipper effect, additional applications of laser may be necessary at two- to three-month intervals. Reabsorption of subretinal fluid may take several months or longer after closure of the outer layer breaks.

Should photocoagulation fail, several management options have been demonstrated to be useful. Retinal cryopexy supplemented by laser photocoagulation, drainage of subretinal fluid, and intraocular gas injection succeeded in both eyes of Case 1. The previously described technique of simultaneous external drainage of subretinal fluid and intraocular gas injection may be a useful adjunct to this.<sup>8</sup> Vitrectomy, internal or external drainage of subretinal and retinoschisis fluid, fluid-gas exchange, and endolaser photocoagulation also appear to offer good results.

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# A Multicenter Study of *Pneumocystis* Choroidopathy

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We studied 21 patients with the acquired immunodeficiency syndrome and presumed *Pneumocystis carinii* choroidopathy. The lesions were characteristically yellow to pale yellow in color, appeared at the level of the choroid, and were found in the posterior pole. They varied in size from 300 to 3,000  $\mu\text{m}$ , initially increasing in number before treatment and eventually resolving after systemic antimicrobial therapy. Of the 21 patients, 18 (86%) had received inhaled pentamidine as prophylaxis against *Pneumocystis pneumonia*. Visual acuity and visual field testing showed little evidence of retinal destruction. Survival after the diagnosis of the choroidopathy ranged from two to 36 weeks. *Pneumocystis* choroidopathy offers an easily accessible clue to disseminated *Pneumocystis* infection. When comparing drugs for *Pneumocystis* prophylaxis, careful ocular examination can provide one indicator of the relative efficacy of protection against extrapulmonary disease.

*PNEUMOCYSTIS CARINII* pneumonia is the most common opportunistic infection in patients with the acquired immunodeficiency syndrome. *Pneumocystis* pneumonia affects more than 80% of patients with AIDS and is the initial manifestation of AIDS in more than 60% of patients.<sup>1,2</sup> This condition is caused by the opportunistic protozoan *P. carinii*, which is a

unicellular parasite. The organism exists exclusively in the extracellular space, and clinical infection is usually limited to the lungs.<sup>3</sup> The diagnosis is usually made by demonstrating the organism in pulmonary specimens.

Extrapulmonary *Pneumocystis* infection has been reported in cases of immunodeficiency, including AIDS.<sup>4-21</sup> The extrapulmonary sites of involvement include the lymph nodes, spleen, liver, bone marrow, small intestine, pericardium, myocardium, hard palate, periureteral soft tissues, and the choroid.

The choroidal infection was first reported histopathologically in an autopsy series by Rao and associates<sup>22</sup> in three patients with AIDS who clinically demonstrated characteristic yellow choroidal infiltrates. This report was followed by the demonstration by Freeman and associates<sup>23</sup> of *P. carinii* organisms in a choroidal biopsy specimen from a patient with AIDS who had clinically similar choroidal lesions. Macher and associates<sup>24</sup> had previously described a patient with AIDS and disseminated *Pneumocystis* infection in whom organisms were found in the choroid at autopsy, but there was no clinical correlation.

The treatment of *Pneumocystis* pneumonia in patients with AIDS with trimethoprim-sulfamethoxazole or intravenous pentamidine is initially effective in most patients; however, more than 60% of patients have a recurrence within 18 months unless prophylactic treatment is instituted.<sup>25</sup> Inhaled pentamidine is widely used as prophylaxis and appears to be effective in preventing recurrent *Pneumocystis* pneumonia in patients with AIDS.<sup>26,27</sup> Aerosolized pentamidine may modify the pulmonary infection; however, it does not eliminate the systemic spread of the organism.<sup>28</sup> Recognition of choroidal infiltration by *P. carinii* is an important and accessible indication of systemic dissemination of the parasite.

We reviewed a large series of patients with *Pneumocystis* choroidopathy to determine the demographic and clinical characteristics of the disease. We evaluated the effect of the lesions

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on visual acuity, their rate of growth and response to therapy, and their fluorescein angiographic characteristics.

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### Patients and Methods

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We studied the medical and ophthalmologic records of 21 patients with *P. carinii* choroidopathy diagnosed at three different medical centers. The dates of AIDS diagnosis and of first *Pneumocystis* pneumonia episode, medications used as prophylaxis against the pneumonia, associated systemic and ocular infections, and the dates of death were all gathered by chart review. All patients were followed up clinically by indirect ophthalmoscopy and fundus photography. Fluorescein angiography was performed in seven patients when the choroidopathy was initially diagnosed. Visual field studies were performed in four patients. Visual fields were studied in conjunction with color fundus photography. The size of each lesion and its location were determined from fundus photography and converted to degrees using the optic nerve head for measurements (vertical axis 7 degrees and horizontal axis 5 degrees; equivalent to  $1.5 \times 1.0$  mm). Automated perimetry was performed in four patients by using the Humphrey 24-2 program (Allergan Humphrey Inc., San Leandro, California) in one patient (6-degree resolution) and by superimposing the 30-1 and 30-2 programs in three patients (3-degree resolution). Histopathologic confirmation of *Pneumocystis* choroidopathy was obtained in two patients, one of whom was described previously.<sup>22</sup>

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### Results

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Of the 21 patients, there were 20 men and one woman, ranging in age from 27 to 47 years. Eight patients were treated with systemic trimethoprim-sulfamethoxazole for their initial *Pneumocystis* pneumonia; three patients received intravenous pentamidine; one patient was treated with trimethoprim-sulfamethoxazole and then intravenous pentamidine; and one patient received dapsone and pyrimethamine as the initial treatment. One patient never had *Pneumocystis* pneumonia but re-

ceived inhaled pentamidine for ten months before the diagnosis of the choroidopathy. In seven patients, the regimen used to treat the initial episode of *Pneumocystis* pneumonia was not known. Of the 21 patients with *Pneumocystis* choroidopathy, 18 were receiving inhalational pentamidine prophylaxis at the time of diagnosis of ocular involvement. Two patients with choroidal *Pneumocystis* had not received inhaled pentamidine. In one patient, it was not possible to determine whether inhalational pentamidine had been received (Table). The average length of time between the diagnosis of *Pneumocystis* choroidopathy and death was four months (range, 0.5 to nine months). Two patients were alive at nine months and five months after the diagnosis of the choroidopathy. The average length of time between the initial *Pneumocystis* pneumonia episode and the choroidopathy was 15.6 months. In two patients, the choroidopathy was diagnosed at the time of *Pneumocystis* pneumonia. The average length of time between the start of inhaled pentamidine and the diagnosis of the choroidopathy was 12.4 months.

The choroidal lesions were characteristically round with irregular borders (Fig. 1). In two patients they appeared confluent. The lesions were bilateral in 16 patients (76%) and unilateral in five (24%). One patient had lesions in one eye but eventually developed bilateral disease. The lesions appeared yellow initially and became pale yellow in appearance while resolving. The size of the lesions varied from 300 to 3,000  $\mu$ m. The number of lesions varied from two to 50 per eye. In 15 of 37 affected eyes (40.5%), the lesions were within the temporal vascular arcades, within 1 disk diameter of the optic nerve head, or both, but not anterior to the posterior pole. In 20 affected eyes (54%), the lesions were posterior to the equator, including the posterior pole. In two affected eyes (5.5%), the lesions were only present between the posterior pole and the equator. No lesions were seen anterior to the equator. No vitreous reaction was seen except in patients with associated cytomegalovirus retinitis.

By using the disk diameter as a reference and assuming it to be  $1.5 \times 1.0$  mm, we compared serial fundus photographs of corresponding retinal fields in six patients. The borders of the untreated lesions appeared to advance in all directions at a rate of 750  $\mu$ m per month (range, 132 to 1,500  $\mu$ m per month)(Fig. 2). Five patients demonstrated an increase in the number of lesions during the first month of observation.



TABLE  
SUMMARY OF THE DRUG REGIMEN USED FOR TREATMENT OF *PNEUMOCYSTIS CARINII* PNEUMONIA\*

CASE NO.	TREATMENT FOR FIRST <i>PNEUMOCYSTIS</i> PNEUMONIA	NO. OF RECURRENCES	TREATMENT OF RECURRENCES	PROPHYLAXIS
1	Trimethoprim-sulfamethoxazole	2	Intravenous pentamidine, trimethoprim-sulfamethoxazole	Inhaled pentamidine
2	Trimethoprim-sulfamethoxazole then pentamidine	3	Intravenous pentamidine, dapsone	Inhaled pentamidine
3	NA	1	NA	NA
4	Trimethoprim-sulfamethoxazole	2	Dapsone, trimethoprim-sulfamethoxazole	Inhaled pentamidine
5	NA	1	NA	Inhaled pentamidine
6	Trimethoprim-sulfamethoxazole	1	NA	Inhaled pentamidine
7	NA	1	NA	Inhaled pentamidine
8	Trimethoprim-sulfamethoxazole	3	Dapsone	Inhaled pentamidine
9	Intravenous pentamidine	0	—	Inhaled pentamidine
10	NA	2	Intravenous pentamidine	Inhaled pentamidine
11†	Intravenous pentamidine	0	Intravenous pentamidine	Inhaled pentamidine
12	Intravenous pentamidine	0	—	Inhaled pentamidine
13	NA	3	NA	Inhaled pentamidine
14†	Dapsone, pyrimethamine	NA	Dapsone, trimethoprim-sulfamethoxazole, intravenous pentamidine	Inhaled pentamidine
15	NA	5	NA	Inhaled pentamidine
16	NA	3	Intravenous pentamidine	Inhaled pentamidine
17	Trimethoprim-sulfamethoxazole	0	—	None
18	Trimethoprim-sulfamethoxazole	0	—	Inhaled pentamidine
19	Never had <i>Pneumocystis</i> pneumonia	0	—	Inhaled pentamidine
20	Trimethoprim-sulfamethoxazole	0 until after <i>Pneumocystis</i> choroidopathy diagnosis	None	None
21	Trimethoprim-sulfamethoxazole	1	Trimethoprim-sulfamethoxazole	Inhaled pentamidine

\*NA indicates not available.

†Previously reported by Freidberg and associates.<sup>33</sup>

In five patients, the lesions disappeared during a period of four months. One of these patients was given intravenous pentamidine one month before the diagnosis of the choroidopathy to treat systemic dissemination of *P. carinii*. The other three patients were treated with intravenous pentamidine after the diagnosis of the choroidopathy with resolution of the lesions during a period of six weeks to four months (Fig. 3). In one patient, we observed resolution of the lesions, but precise information about intravenous pentamidine treatment could not be obtained.

Fluorescein angiograms in seven patients disclosed early hypofluorescence corresponding to the lesions with late staining of the lesions, which appeared deep to the retinal circulation (Fig. 4). Four patients were tested with automated perimetry, with attention directed to the

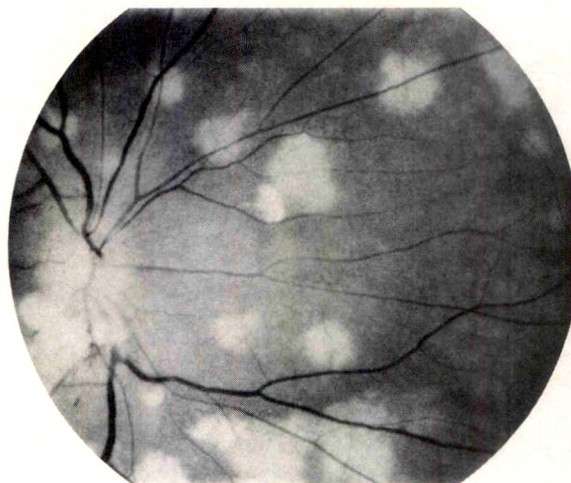
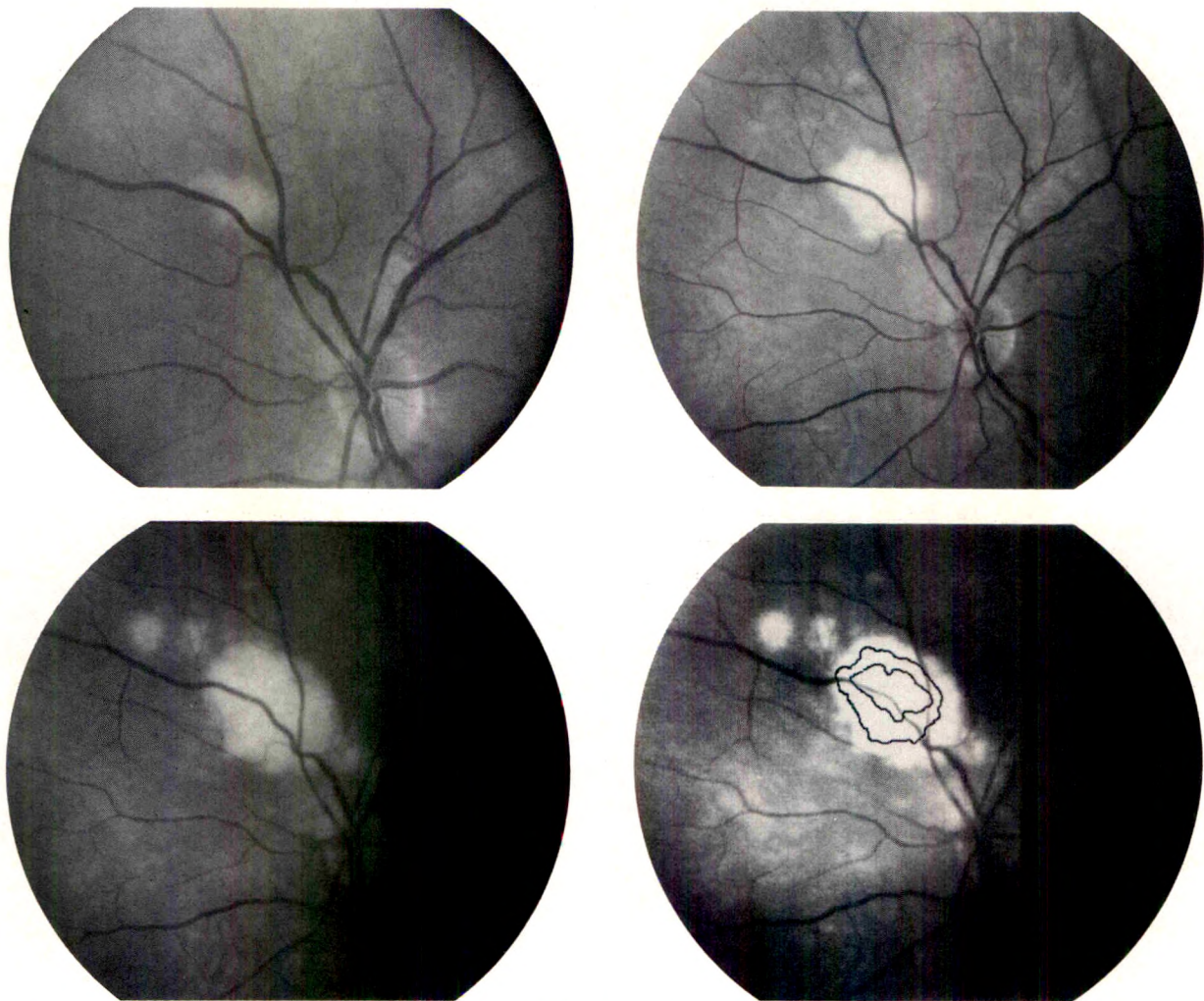


Fig. 1 (Shami and associates). Choroidal infiltrates secondary to *P. carinii* in a 41-year-old man. The lesions are round with irregular borders.





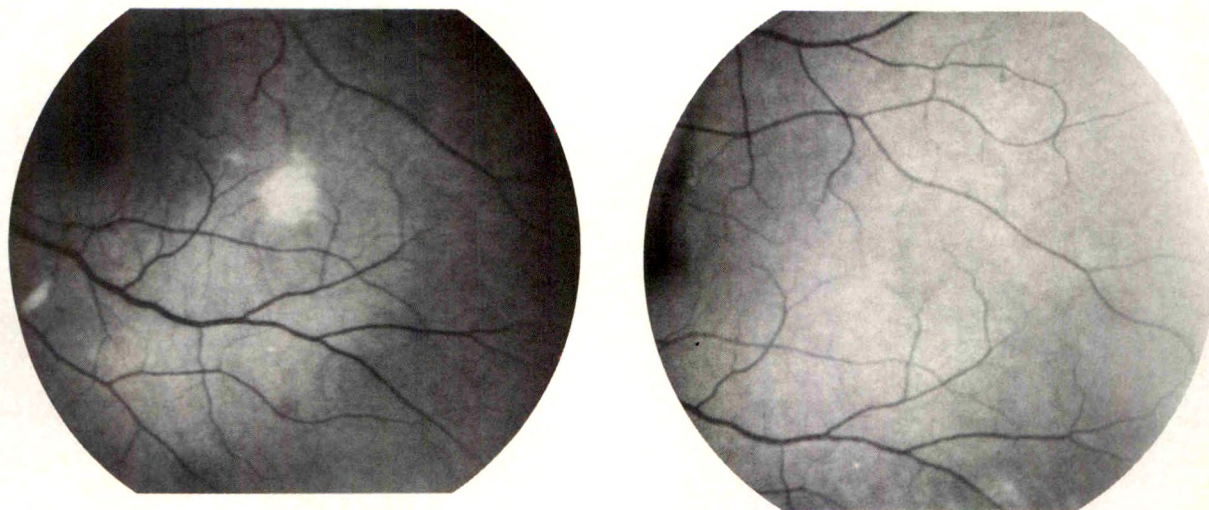
**Fig. 2** (Shami and associates). Top left, Jan. 23, 1989. Choroidal *Pneumocystis* lesion superonasal to optic nerve head in left eye. A resolving cotton-wool spot with small intraretinal hemorrhages is seen 1,000  $\mu\text{m}$  from the optic nerve head superotemporally. Top right, March 8, 1989. Six weeks later, the *Pneumocystis* lesion has increased in size and the lesion has become denser in appearance. A new lesion has appeared superior to the large lesion. Lower left, April 20, 1989. A total of 12 weeks after the initial photograph, the largest *Pneumocystis* lesion has increased in size and three new satellite lesions are seen, one at the inferotemporal edge of the largest lesion and two superonasal to it. Lower right, A digital, size- and orientation-corrected montage of these three photographs. The black circles represent the borders of the main *Pneumocystis* lesion at six-week intervals. The area of the lesion has more than doubled in 12 weeks with the borders advancing at a rate between 200 and 1,000  $\mu\text{m}$  in each six-week interval (33 to 167  $\mu\text{m}$  per week).

areas of choroidal involvement. In one patient a depression of 8 to 11 dB over the lesions was found with good reliability indices (Fig. 5). A second patient demonstrated a depression of 6 to 8 dB over some but not all lesions in both eyes. Automated perimetry in the other two patients did not show any defect over the lesions.

## Discussion

The recent recognition of *Pneumocystis* choroidopathy is important in the treatment of immunosuppressed patients. We studied a large number of patients with *Pneumocystis* choroidopathy to understand the clinical characteris-





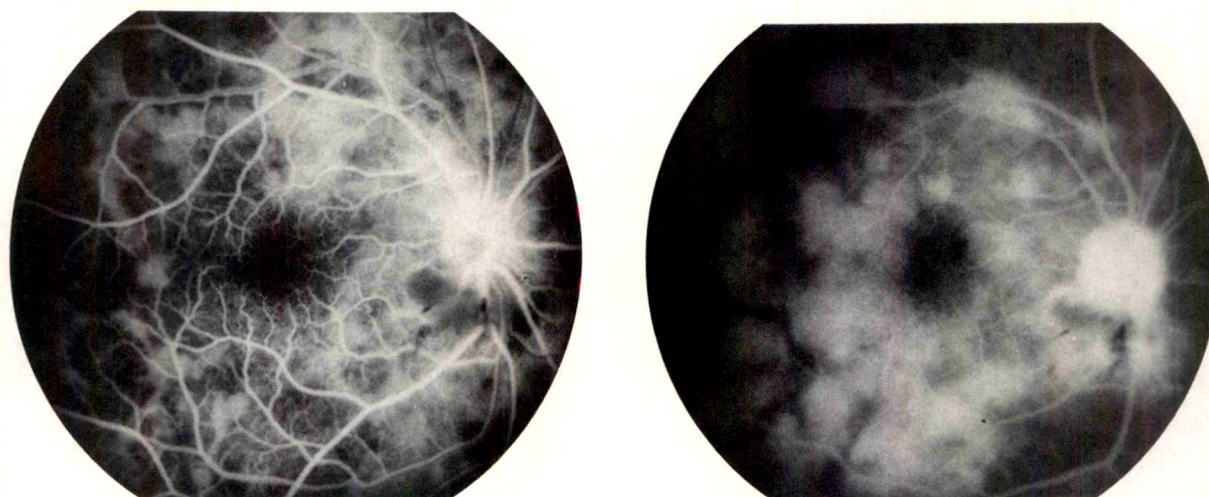
**Fig. 3** (Shami and associates). Left, July 27, 1989. Choroidal *Pneumocystis* lesion temporal to the macula. Right, Nov. 10, 1989. The lesion has almost completely resolved after intravenous pentamidine treatment.

tics of the disease, the response of the lesions to treatment, and the visual consequences of the infection.

Our study shows that *Pneumocystis* lesions are typically yellow in color and are usually round with irregular borders. In some cases, the lesions progressed and became confluent. The choroidal infiltrates were not associated with any vitreous inflammation unless other infectious retinitis was present. All lesions were located posterior to the equator.

In four patients, we observed resolution dur-

ing a period of six weeks to four months after intravenous pentamidine treatment. One of those patients was treated with intravenous pentamidine for systemic pneumocystosis before the diagnosis of the choroidopathy. In this patient, the resolution of the lesions appeared to result from this treatment; the infiltrates were probably present before the date the patient was referred to us. The other three patients were treated with intravenous pentamidine after the diagnosis of the choroidopathy. Extrapulmonary *Pneumocystis* infection is in-



**Fig. 4** (Shami and associates). Left, Early-phase transit of the right eye of a patient with subfoveal *Pneumocystis* choroidal infiltrates shows hypofluorescence corresponding to the lesion. Right, Late phase of the study shows staining of the choroidal lesions.



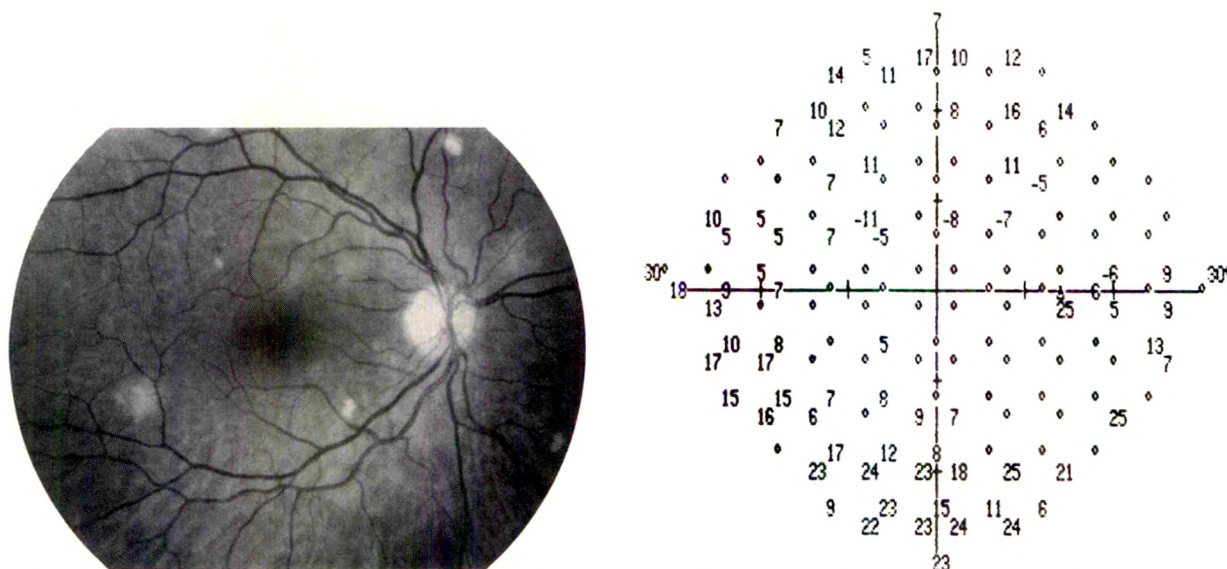


Fig. 5 (Shami and associates). Left, *Pneumocystis* choroidal infiltrate inferotemporal to the fovea. Right, Automated perimetry superimposing the 30-1 and 30-2 programs shows a depression of 8 to 11 dB corresponding to the choroidal infiltrate shown on the fundus photograph.

creasingly recognized in patients with AIDS receiving inhaled pentamidine prophylaxis, since after aerosolized administration the drug is recovered exclusively from the lungs with little extrapulmonary distribution.<sup>27</sup> Furthermore, aerosol pentamidine does not always distribute equally throughout the lungs, and upper lobe *Pneumocystis* pneumonia is becoming an increasingly common event.<sup>29</sup> This may allow the extrapulmonary spread of the organism to distant organs, including the choroid.

One of our patients never had *Pneumocystis* pneumonia but was taking aerosol pentamidine prophylaxis. This suggests that the aerosol pentamidine might have been an effective prophylaxis against the pneumonia, but it allowed extrapulmonary spread of the protozoan as implicated by the choroidopathy. Two of our patients who gave a history of *Pneumocystis* pneumonia, but who had received no inhaled pentamidine prophylaxis, demonstrated the presence of choroidal infection, which suggest-

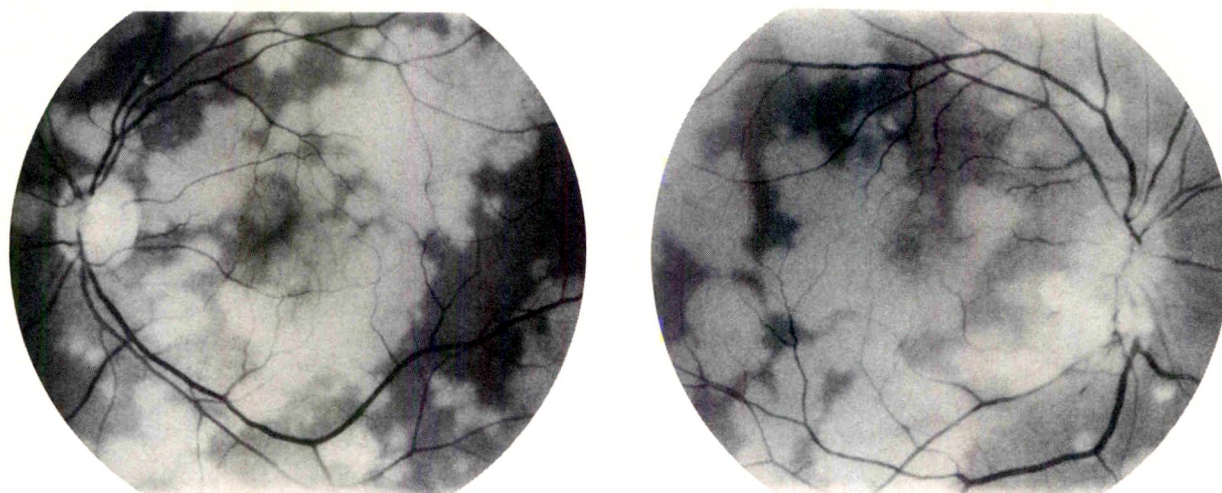


Fig. 6 (Shami and associates). Subfoveal choroidal infiltrate secondary to *Pneumocystis carinii* in a patient who maintained visual acuity of 20/20 in both eyes.



ed that extrapulmonary spread might have occurred at the time of the initial infection despite treatment with trimethoprim-sulfamethoxazole. The recognition of *Pneumocystis* choroidopathy as a sign of systemic dissemination of the protozoan makes ocular examination imperative before assuming the infection to be confined to the lungs and possibly amenable to treatment with inhaled pentamidine alone.<sup>30</sup> Dugel and associates<sup>31</sup> reported the resolution of the choroidal lesions during three weeks in two patients, one treated with intravenous trimethoprim-sulfamethoxazole and the other with intravenous pentamidine. Koser, Jampol, and MacDonnell<sup>32</sup> observed a much slower regression of the lesions in their patients treated with systemic anti-*Pneumocystis* therapy. Although systemic treatment can be considered when the diagnosis of choroidopathy is made, it is not yet clear whether the resolution of the lesions could be used as an indicator of eradication of all sites of extrapulmonary infection. The true incidence of *Pneumocystis* choroidopathy cannot be determined from our study, because the infection appears to be asymptomatic and the lesions were incidentally detected in patients who were referred for examination.

Angiographically, the lesions demonstrated hypofluorescence at the level of the choroid in the early phases and stained late. This is compatible with the foamy eosinophilic space occupying lesions seen histopathologically. In our series, the choroidal infiltrates were not associated with decrease in visual acuity despite the presence of a subfoveal lesion in one patient who maintained visual acuity of 20/20 (Fig. 6). The visual fields, however, demonstrated a depression over areas corresponding to the choroidal infiltrates in two patients. The depressions appear to be of a mild degree, a finding compatible with the histopathologic changes, which demonstrate infiltration of the choroid and the choriocapillaris with no destruction of the overlying neurosensory retina.<sup>22</sup>

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## Detection of Antibodies Against *Borrelia burgdorferi* in Patients With Uveitis

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We determined the antibody response against *Borrelia burgdorferi* strains isolated from Japanese *Ixodes ovatus* and *Ixodes persulcatus* ticks by enzyme-linked immunosorbent assay and indirect immunofluorescence assay of serum specimens from 127 patients with uveitis. We examined samples of serum from Japanese patients with unclassified uveitis, iridocyclitis caused by herpes zoster virus, Behçet's disease, Vogt-Koyanagi-Harada syndrome, sarcoidosis, or other conditions (sympathetic ophthalmia, Posner-Schlossman syndrome and acute anterior uveitis with ankylosing spondylitis). Serum from healthy individuals and patients with Lyme disease served as negative and positive control samples, respectively. Significantly higher antibody titers were demonstrated in patients with uveitis than in control subjects. Of 29 patients with unclassified uveitis, nine (31) had significantly increased antibody titers against *B. burgdorferi* strain H014 by ELISA testing. Five patients also showed higher IgG and IgM responses than in three control subjects with Lyme disease. All positive controls showed joint problems characteristic of rheu-

matoid arthritis. One of three patients had uveitis. The patients were diagnosed as having Lyme disease on the basis of their history and serologic tests. A positive antibody response was recognized in several patients with Behçet's disease, Vogt-Koyanagi-Harada syndrome, sarcoidosis, and other conditions (acute anterior uveitis with ankylosing spondylitis), but not in control subjects.

LYME DISEASE is a tick-transmitted spirochetosis,<sup>1</sup> first reported in 1977 in Connecticut.<sup>2</sup> Lyme disease is characterized by a distinctive skin lesion, erythema chronicum migrans, which is often accompanied by constitutional symptoms. Ocular manifestations have been reported infrequently, but as the disease is increasing in frequency and occurring in new geographic areas,<sup>3</sup> more cases with ocular involvement can be expected. Winward and associates<sup>4</sup> reported the ocular findings in patients with Lyme disease. In ophthalmic disease with uveitis, the prognosis is poor, and the cause of the disease is unclear. We obtained sera from patients with uveitis in the endemic area of Japan and analyzed immunoglobulin levels against *Borrelia burgdorferi*.

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### Patients and Methods

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The serum specimens from 127 patients with uveitis were examined. Unclassified uveitis was observed in 29 patients, iridocyclitis caused by herpes zoster virus in two patients, Behçet's disease in 35 patients, Vogt-Koyanagi-Harada syndrome in 28 patients, sarcoidosis in 16 patients, and other conditions (sympathetic ophthalmia, Posner-Schlossman syndrome, and acute anterior uveitis with ankylosing spondy-



litis) in 17 patients. Forty-four healthy individuals served as negative control subjects; they had no history of Lyme disease and no clinical signs to associate with the disease. Three positive controls showed joint problems characteristic of rheumatoid arthritis and one had uveitis. They were diagnosed as having Lyme disease on the basis of aspects of their history, such as tick contacts, erythema chronicum migrans, and serologic tests.

The two Japanese strains, H014 and HP3, which were isolated from the midgut of *Ixodes ovatus* and *I. persulcatus* in Hokkaido, Japan, in 1989,<sup>5</sup> were used for the study. *Borrelia* species strains were cultivated in BSK II medium at 32 C for five to seven days by the method of Burgdorfer and associates.<sup>6</sup>

Enzyme-linked immunosorbent assay was done by the method previously described.<sup>7</sup> The antigen preparation was performed by the method of Russell and associates.<sup>8</sup> The bacterial strains grown in the medium were pelleted by centrifugation at  $10,000 \times g$  for 20 minutes and washed three times in phosphate-buffered saline (pH 7.2). The final pellet was suspended in carbonate buffer (0.05 M, pH 9.6) and then sonicated on ice three times for 30 seconds each time. After determination of protein concentration by the Bio-Rad protein assay kit (Bio-Rad Laboratories, Richmond, California), it was adjusted at 10  $\mu\text{g}/\text{ml}$ .

Enzyme-linked immunosorbent assay microplates were coated overnight at 4 C. After repeated washing, 100  $\mu\text{l}$  of the serum sample diluted 1:100 in phosphate-buffered saline was added, and the plates were incubated for one hour at 37 C for both IgG and IgM. Peroxidase-conjugated antihuman IgG (100  $\mu\text{l}$ , goat IgG fraction, Cappel Co. Ltd., Malvern, Pennsylvania) diluted 1:500, or IgM (100  $\mu\text{l}$ , goat IgG fraction, Cappel Co. Ltd.) diluted 1:200 in phosphate-buffered saline with 0.05% Tween 20 and 10% Block Ace (Yukijirushi Co., Ltd., Japan), was added to each well, and the plates were incubated at 37 C for one hour. A concentration of 100  $\mu\text{l}$  of o-phenylenediamine (4 mg/ml) in 0.1-M citrate-phosphate buffer (pH 5.0) containing 0.02% hydrogen peroxide was added to each well. The colorimetric value was determined by an ELISA reader (MTP-22, Corona Electric Co. Ltd., Ibaragi, Japan) with absorbance value at 492 nm. All plates were washed at least five times in phosphate-buffered saline with 0.05% Tween 20 and 10% Block Ace. Standardization of ELISA was done by the

method described previously.<sup>7</sup> For comparison with our ELISA diagnostic system, the Human Lyme Enzyme Immunoassay kit (Cambridge BioScience, Cambridge, Massachusetts) was used to detect antibodies to *B. burgdorferi* American strain B31.

Indirect immunofluorescence assay was used to detect the IgG or IgM antibody against *B. burgdorferi* H014 in ELISA-positive sera. The indirect immunofluorescence assay testing was done by the method of Russell and associates.<sup>8</sup> Briefly, the washed spirochetes were diluted in phosphate-buffered saline to 100 to 200 organisms per  $40\times$  microscope field. Multiwell immunofluorescence slides (Flow Laboratory, U.S.A.) were coated with 20  $\mu\text{l}$  of the organisms per well. The slides were air-dried for 15 minutes at room temperature, fixed in ice-cold acetone for 10 minutes, and air-dried again. The serial twofold diluted serum was placed on a well of fixed antigen, and the slides were incubated in a moist chamber at 37 C for 30 minutes. The slides were rinsed quickly, soaked in phosphate-buffered saline for 10 minutes, and blotted gently. A 20- $\mu\text{l}$  volume of fluorescein isothiocyanate-labeled goat antihuman IgG (Cappel Co. Ltd.) and goat antihuman IgM (Cappel Co. Ltd.) was placed on each slide well, and the slides were incubated, rinsed, and dried as before. Slides were covered with mounting fluid and examined by fluorescence microscopy. A titer of more than 1:64 was considered to be positive with reference to the report of Magnarelli and associates.<sup>9</sup> Titer of each positive control in this study was 1:124.

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## Results

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Serum specimens were tested by ELISA. IgG antibody to *B. burgdorferi* H014 was detected in nine of 29 patients with unclassified uveitis (31%), six of 35 patients with Behçet's disease (17.1%), two of 16 patients with sarcoidosis (12.5%), and one of 17 patients with other conditions (5.9%). IgM antibody to the strain was detected in four patients with unclassified uveitis (13.8%), five patients with Behçet's disease (14.3%), one patient with Vogt-Koyanagi-Harada syndrome (3.6%), and one patient with sarcoidosis (6.3%) (Table 1). Antibodies to the strain HP3 were also detected in 12 of the 19 serum samples obtained from the patients with positive reactions to the strain H014 (Table 2).



**TABLE 1**  
APPEARANCE OF ANTIBODIES AGAINST *B. BURGDORFERI* H014 IN PATIENTS WITH UVEITIS

DISEASE	NO. OF PATIENTS	IgG		IgM	
		ELISA* POSITIVE	IFA* POSITIVE	ELISA* POSITIVE	IFA* POSITIVE
Unclassified uveitis	29	9 (31.0)*	14 (48.3)	4 (13.8)	4 (13.8)
Iridocyclitis	21	9 (42.9)	12 (57.1)	3 (14.3)	3 (14.3)
Uveoretinitis	3	0 ( 0 )	2 (66.7)	1 (33.3)	1 (33.3)
Panuveitis	5	0 ( 0 )	0 ( 0 )	0 ( 0 )	0 ( 0 )
Iridocyclitis caused by herpes zoster virus	2	0 ( 0 )	0 ( 0 )	0 ( 0 )	0 ( 0 )
Behçet's disease	35	6 (17.1)	7 (20.0)	5 (14.3)	5 (14.3)
Vogt-Koyanagi-Harada disease	28	0 ( 0 )	4 (14.3)	1 ( 3.6)	1 ( 3.6)
Sarcoidosis	16	2 (12.5)	4 (25.0)	1 ( 6.3)	1 ( 6.3)
Others†	17	1 ( 5.9)	2 (11.8)	0 ( 0 )	0 ( 0 )
Healthy controls	44	0 ( 0 )	0 ( 0 )	0 ( 0 )	0 ( 0 )

\*Enzyme-linked immunosorbent assay.

†Immunofluorescence assay.

\*No. (%).

†Sympathetic ophthalmia, Posner-Schlossman syndrome and acute anterior uveitis with ankylosing spondylitis.

No antibodies were observed in the sera from patients with iridocyclitis caused by herpes zoster virus or control subjects.

To confirm ELISA-positive serum, indirect immunofluorescence assay testing was done. All of the serum to *B. burgdorferi* H014 showed a positive reaction to indirect immunofluores-

cence assay, and the positive percentage was larger than that in the ELISA system (Table 1).

Significant amounts of IgG or IgM antibody were distinctly distributed in the seropositive groups (seropositive groups compared with healthy control subjects,  $P < .01$ ) (Table 3). No healthy control subjects showed antibodies to

**TABLE 2**  
APPEARANCE OF ANTIBODIES AGAINST *B. BURGDORFERI* HP3 IN PATIENTS WITH UVEITIS

DISEASE	NO. OF PATIENTS	ELISA* POSITIVE NUMBER (%)	
		IgG	IgM
Unclassified uveitis	29	6 (20.7)	5 (17.2)
Iridocyclitis	21	5 (23.8)	3 (14.3)
Uveoretinitis	3	1 (33.3)	1 (33.3)
Panuveitis	5	0 ( 0 )	1 (20.0)
Iridocyclitis caused by herpes zoster virus	2	0 ( 0 )	0 ( 0 )
Behçet's disease	35	3 ( 8.6)	3 ( 8.6)
Vogt-Koyanagi-Harada disease	28	2 ( 7.1)	2 ( 7.1)
Sarcoidosis	16	1 ( 6.3)	3 (18.8)
Others*	17	2 (11.8)	0 ( 0 )
Healthy controls	44	0 ( 0 )	0 ( 0 )

\*Enzyme-linked immunosorbent assay

\*Sympathetic ophthalmia, Posner-Schlossman syndrome and acute anterior uveitis with ankylosing spondylitis.



**TABLE 3**  
LEVEL OF IgM ANTIBODY AGAINST *B. BURGDORFERI* H014 IN PATIENTS WITH UVEITIS (ENZYME-LINKED IMMUNOSORBENT ASSAY)

LEVEL OF IGM ANTIBODY AGAINST <i>B. BURGDORFERI</i> H014 (COLORIMETRIC VALUE; MEAN $\pm$ S. D.)			
DISEASE	TOTAL	ANTIBODY NEGATIVE GROUP	ANTIBODY POSITIVE GROUP
Unclassified uveitis	0.334 $\pm$ 0.396	0.188 $\pm$ 0.161	1.247 $\pm$ 0.155
Iridocyclitis	0.328 $\pm$ 0.365	0.205 $\pm$ 0.164	1.183 $\pm$ 0.107
Uveoretinitis	0.644 $\pm$ 0.688	0.246	1.438
Panuveitis	0.149 $\pm$ 0.199	0.149 $\pm$ 0.199	No*
Iridocyclitis caused by herpes zoster virus	0.190	0.190	No
Behçet's disease	0.342 $\pm$ 0.422	0.154 $\pm$ 0.173	1.024 $\pm$ 0.092
Vogt-Koyanagi-Harada disease	0.198 $\pm$ 0.252	0.163 $\pm$ 0.176	1.152
Sarcoidosis	0.185 $\pm$ 0.208	0.157 $\pm$ 0.136	0.845
Others*	0.112 $\pm$ 0.133	0.112 $\pm$ 0.133	No
Lyme disease (Postive control)	0.898 $\pm$ 0.050	No	0.898 $\pm$ 0.050
Healthy controls	0.145 $\pm$ 0.071	0.145 $\pm$ 0.071	No

\*No samples.

\*Sympathetic ophthalmia, Posner-Schlossman syndrome, and acute anterior uveitis with ankylosing spondylitis.

strains of *B. burgdorferi*. There were no significant differences between the seronegative group and the healthy control subject group in the detection system of IgM antibody against the strain H014 (Table 3). The antibody levels

of some seronegative groups of patients were significantly higher than that of the healthy control subject group in the detection system of IgG antibody against the strain H014 (Table 4). Similar results were obtained in the system for

**TABLE 4**  
LEVEL OF IgG ANTIBODY AGAINST *B. BURGDORFERI* H014 IN PATIENTS WITH UVEITIS (ENZYME-LINKED IMMUNOSORBENT ASSAY)

LEVEL OF IGG ANTIBODY AGAINST <i>B. BURGDORFERI</i> H014 (COLORIMETRIC VALUE; MEAN $\pm$ S. D.)			
DISEASE	TOTAL	ANTIBODY NEGATIVE GROUP	ANTIBODY POSITIVE GROUP
Unclassified uveitis	0.717 $\pm$ 0.376	0.548 $\pm$ 0.298	1.049 $\pm$ 0.227
Iridocyclitis	0.723 $\pm$ 0.405	0.536 $\pm$ 0.293	1.094 $\pm$ 0.227
Uveoretinitis	0.535 $\pm$ 0.466	0.535 $\pm$ 0.466	No*
Panuveitis	0.539 $\pm$ 0.192	0.539 $\pm$ 0.192	No
Iridocyclitis caused by herpes zoster virus	0.679	0.679	No
Behçet's disease	0.645 $\pm$ 0.320	0.558 $\pm$ 0.288	1.223 $\pm$ 0.269
Vogt-Koyanagi-Harada disease	0.400 $\pm$ 0.341	0.400 $\pm$ 0.341	No
Sarcoidosis	0.526 $\pm$ 0.383	0.463 $\pm$ 0.354	1.061
Others*	0.592 $\pm$ 0.353	0.540 $\pm$ 0.297	1.363
Lyme disease (Postive control)	0.912 $\pm$ 0.051	No	0.912 $\pm$ 0.051
Healthy controls	0.112 $\pm$ 0.134	0.112 $\pm$ 0.134	No

\*No samples.

\*Sympathetic ophthalmia, Posner-Schlossman syndrome, and acute anterior uveitis with ankylosing spondylitis.



**TABLE 5**  
LEVEL OF IgM ANTIBODY AGAINST *B. BURGDORFERI* HP3 IN PATIENTS WITH UVEITIS (ENZYME-LINKED IMMUNOSORBENT ASSAY)

LEVEL OF IgM ANTIBODY AGAINST <i>B. BURGDORFERI</i> HP3 (COLORIMETRIC VALUE; MEAN $\pm$ S. D.)			
DISEASE	TOTAL	ANTIBODY NEGATIVE GROUP	ANTIBODY POSITIVE GROUP
Unclassified uveitis	0.608 $\pm$ 0.407	0.460 $\pm$ 0.244	1.322 $\pm$ 0.229
Iridocyclitis	0.615 $\pm$ 0.389	0.495 $\pm$ 0.250	1.370 $\pm$ 0.200
Uveoretinitis	0.755 $\pm$ 0.657	0.390	1.484
Panuveitis	0.405 $\pm$ 0.363	0.254 $\pm$ 0.149	1.012
Iridocyclitis caused by herpes zoster virus	0.447	0.447	No*
Behçet's disease	0.405 $\pm$ 0.326	0.343 $\pm$ 0.262	1.073 $\pm$ 0.082
Vogt-Koyanagi-Harada disease	0.390 $\pm$ 0.413	0.296 $\pm$ 0.235	1.612
Sarcoidosis	0.477 $\pm$ 0.478	0.291 $\pm$ 0.243	1.340 $\pm$ 0.295
Others <sup>†</sup>	0.320 $\pm$ 0.201	0.320 $\pm$ 0.201	No
Lyme disease (Positive control)	1.079 $\pm$ 0.286	No	1.079 $\pm$ 0.286
Healthy controls	0.180 $\pm$ 0.085	0.180 $\pm$ 0.085	No

\*No samples.

<sup>†</sup>Sympathetic ophthalmia, Posner-Schlossman syndrome and acute anterior uveitis with ankylosing spondylitis.

strain HP3 (Tables 5 and 6). Most of the positive serum in patients showed higher levels than that of patients with Lyme disease. Five of nine patients with unclassified uveitis showed high-

er IgG and IgM response than did the three positive controls with Lyme disease. A positive antibody response against H014 was recognized in several patients with Behçet's disease

**TABLE 6**  
LEVEL OF IgG ANTIBODY AGAINST *B. BURGDORFERI* HP3 IN PATIENTS WITH UVEITIS (ENZYME-LINKED IMMUNOSORBENT ASSAY)

LEVEL OF IgG ANTIBODY AGAINST <i>B. BURGDORFERI</i> HP3 (COLORIMETRIC VALUE; MEAN $\pm$ S. D.)			
DISEASE	TOTAL	ANTIBODY NEGATIVE GROUP	ANTIBODY POSITIVE GROUP
Unclassified uveitis	0.750 $\pm$ 0.374	0.598 $\pm$ 0.221	1.332 $\pm$ 0.240
Iridocyclitis	0.800 $\pm$ 0.385	0.638 $\pm$ 0.234	1.349 $\pm$ 0.263
Uveoretinitis	0.765 $\pm$ 0.435	0.525	1.246
Panuveitis	0.556 $\pm$ 0.237	0.556 $\pm$ 0.237	No*
Iridocyclitis caused by herpes zoster virus	0.634	0.634	No
Behçet's disease	0.537 $\pm$ 0.341	0.441 $\pm$ 0.216	1.279 $\pm$ 0.148
Vogt-Koyanagi-Harada disease	0.482 $\pm$ 0.294	0.430 $\pm$ 0.229	1.161
Sarcoidosis	0.564 $\pm$ 0.317	0.509 $\pm$ 0.227	1.449
Others <sup>†</sup>	0.550 $\pm$ 0.265	0.481 $\pm$ 0.191	1.071
Lyme disease (Positive control)	0.716 $\pm$ 0.194	No	0.716 $\pm$ 0.194
Healthy controls	0.271 $\pm$ 0.152	0.271 $\pm$ 0.152	No

\*No samples.

<sup>†</sup>Sympathetic ophthalmia, Posner-Schlossman syndrome, and acute anterior uveitis with ankylosing spondylitis.



TABLE 7  
IMMUNOFLUORESCENCE ANTIBODY TITER AGAINST *B. BURGDORFERI* H014 IN PATIENTS WITH UVEITIS

DISEASE	IMMUNOFLUORESCENT ANTIBODY TITER AGAINST <i>B. BURGDORFERI</i> H014 (MEAN $\pm$ S. D.)					
	IGG ANTIBODY			IGM ANTIBODY		
	TOTAL	NEGATIVE	POSITIVE	TOTAL	NEGATIVE	POSITIVE
Unclassified uveitis	5.2 $\pm$ 2.5	3.3 $\pm$ 2.0	7.1 $\pm$ 1.2	3.0 $\pm$ 2.6	2.0 $\pm$ 1.5	8.3 $\pm$ 1.0
Iridocyclitis	5.5 $\pm$ 2.5	3.5 $\pm$ 2.0	7.2 $\pm$ 1.7	3.0 $\pm$ 2.5	1.5 $\pm$ 1.4	7.2 $\pm$ 2.5
Uveoretinitis	4.3 $\pm$ 3.8	ND*	6.5	4.7 $\pm$ 3.8	2.0	6.0
Panuveitis	3.7 $\pm$ 1.2	3.7 $\pm$ 1.2	No <sup>+</sup>	1.0 $\pm$ 1.0	1.0 $\pm$ 1.0	No
Iridocyclitis caused by herpes zoster virus	4.5	4.5	No	1.0	1.0	No
Behçet's disease	4.0 $\pm$ 2.3	3.3 $\pm$ 2.0	6.7 $\pm$ 0.8	2.3 $\pm$ 2.7	1.3 $\pm$ 1.6	7.4 $\pm$ 1.1
Vogt-Koyanagi-Harada disease	2.5 $\pm$ 2.4	2.3 $\pm$ 2.3	6.0	0.9 $\pm$ 1.8	0.7 $\pm$ 1.3	8.0
Sarcoidosis	4.0 $\pm$ 2.6	3.2 $\pm$ 2.3	6.8 $\pm$ 1.0	1.7 $\pm$ 2.1	1.4 $\pm$ 1.9	6.0
Others <sup>‡</sup>	3.7 $\pm$ 2.2	3.2 $\pm$ 2.0	6.5	0.7 $\pm$ 1.1	0.7 $\pm$ 1.1	No
Lyme disease (Positive control)	7.0	No	7.0	7.0	No	7.0
Healthy controls	0.5 $\pm$ 1.0	0.5 $\pm$ 1.0	No	0.5 $\pm$ 0.9	0.5 $\pm$ 0.9	No

\*Not detected.

<sup>+</sup>No samples.

<sup>‡</sup>Sympathetic ophthalmia, Posner-Schlossman syndrome, and acute anterior uveitis with ankylosing spondylitis.

(six of 35), Vogt-Koyanagi-Harada syndrome (one of 28), sarcoidosis (two of 16), and other conditions (one of 17, acute anterior uveitis with ankylosing spondylitis).

In the indirect immunofluorescence assay titer against *B. burgdorferi* H014, significant amounts of antibodies were distributed in the seropositive groups (seropositive groups compared with healthy control subjects,  $P < .01$ ) (Table 7). There were no differences between seronegative groups and healthy control subjects.

The ELISA value and indirect immunofluorescence assay titer were correlated with each other ( $P < .01$ ). The correlation coefficient was .8836 in IgG antibody against H014 and .9607 in IgM antibody against the strain.

A correlation was observed between strain H014 and HP3 (IgG,  $P < .01$ , correlation coefficient .6606; IgM,  $P < .01$ , correlation coefficient .3926) (Table 9). In contrast, there was no correlation between the Japanese strains and American strain B31, with only one exception (correlation between IgG against strain H014 and Ig against strain B31,  $P < .05$ , correlation coefficient .2231).

The IgG level against the Japanese strains was correlated to the IgM level (H014,  $P < .01$ , correlation coefficient .2922; HP3,  $P < .01$ , correlation coefficient .5084). The patients with uve-

itis (especially unclassified uveitis) were in the active stage, and the increased level of IgM may be one of the markers in the active stage.

## Discussion

The cases of unclassified uveitis were probably complications of Lyme disease, because the patients showed positive serum reaction against the bacteria and could remember being bitten by a tick. A close association exists among the distribution of ixodid ticks and human beings with Lyme disease. In Japan, a patient with Lyme disease was described by Kawabata and associates in 1987,<sup>10</sup> and *B. burgdorferi* was isolated from two species of *Ixodes* ticks, *I. persulcatus* and *I. ovatus*.<sup>5</sup> The ticks are now found abundantly in Hokkaido, Japan, and the infection rate of these ixodid ticks with *Borrelia* species in the area is presumed to be 10% to 20% (unpublished data). In tick-infested areas, serologic studies of dogs may be particularly useful in identifying newly established foci of *B. burgdorferi* infection. The percentage of seropositive dogs in Hokkaido (serum samples were obtained from patients and control subjects in the same area) was 20%, and the area was considered to be an endemic area



of Lyme disease.<sup>7</sup> Ophthalmologists should become familiar with the manifestation of Lyme disease in endemic areas since patients have ocular disorders such as iridocyclitis in any stage of the disease.

Immunoassays that detect the presence of antibodies specific for *B. burgdorferi* have been considered the most effective diagnostic tools for Lyme disease.<sup>11</sup> These assays are usually performed by one of two techniques, indirect immunofluorescence assay or ELISA. In our study, the correlation between ELISA and indirect immunofluorescence assay was recognized, and the correlation coefficient was strong. We conclude that measurement of serum antibodies is a highly sensitive and specific method for the immunologic diagnosis of ocular Lyme disease in both ELISA and indirect immunofluorescence assay testing.

Antigenic properties of Japanese strains were different from that of the strains isolated in the United States and Europe (T. Matsuzawa and M. Mori, personal communication, 1990). We determined that the Japanese strains are more suitable for serodiagnosis of Lyme disease as an antigen source in Japan than the American or European strains.

Cross-reactivity occurred in both tests with sera from human patients with other spirochetal diseases, because the causative organisms are taxonomically related, and common antigens have been described for various spirochetes.<sup>12</sup> Zierhut, Kreissig, and Pickert<sup>13</sup> noted that a patient with panuveitis and a positive serologic result for syphilis showed positive test results for Lyme disease. Positive serum against seven serovars of *Leptospira interrogans* was not observed in the sera (data not shown). Therefore, cross-reactivity to *Leptospira* species was not a diagnostic problem in our cases. Serum antibodies to other *Borrelia* and *Treponema* species reacted with *B. burgdorferi* in ELISA and indirect immunofluorescence assay. Our cases were considered to be different from the diseases of borreliosis and syphilis. At least, new world borreliosis and old world borreliosis (tick-borne relapsing fever and louse-borne relapsing fever, respectively) were rare in Hokkaido. These serologic tests can provide laboratory support, with a high degree of specificity and sensitivity, for a diagnosis of ocular Lyme disease in serologic surveys of humans.

In our study, 44 control subjects had no antibodies against *B. burgdorferi*. In serologic tests (indirect immunofluorescence assay), antibodies to the bacteria were positive in 40 of 798

(5.0%) subjects in four regions of Hokkaido.<sup>5</sup> For comparison with this result, the rate of positive reaction in unclassified uveitis (48.2% in indirect immunofluorescence assay) was ten times larger than that of healthy persons (5.0%). Thus, unclassified uveitis in Japan, especially the endemic area, could be correlated to *B. burgdorferi* infection.

Other diseases, such as Behçet's disease, Vogt-Koyanagi-Harada syndrome, and sarcoidosis, may produce cross-reactive antibodies. Our data showed that the seronegative patients also had higher antibody levels to *B. burgdorferi* than the healthy control subjects. There is no other evidence to support any of those considerations in our patients. It has been shown that *B. burgdorferi* expresses the 60-Kilodalton Common Antigen with an equivalent antigen in a wide range of remotely bacteria.<sup>14</sup> The Common Antigen was recently referred to as heat shock protein. Heat shock protein has been shown to be involved in the pathogenesis of autoimmune arthritis.<sup>15,16</sup> The extensive cross reactivity of antigens such as heat shock protein may account for the low diagnostic specificity of the serologic tests in autoimmune-like diseases. We could not distinguish whether the uveitis was the direct result of infection by *B. burgdorferi* or the result of an antigen-antibody reaction or some other immunologic phenomenon in the area.

#### ACKNOWLEDGMENT

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#### OPHTHALMIC MINIATURE

He had got his knock-out in 1918. The bullet had grazed the optic nerve. At first he had gone to a base hospital, but as soon as he could he had come to Paris to be treated by a very celebrated man. He had been in danger of losing the sight of the right eye; it had scared him to death. . . . The oculist had warned him that the trouble might recur, that he ought to have remained under observation. Well, it had recurred about four months ago. He had got the wind up and rushed back to Paris. For three weeks he had lain in a darkened room, not daring to think of the possible verdict. Eyes were so tiresomely sympathetic: if the one went the other might easily follow.

Radclyffe Hall, *The Well of Loneliness*  
New York, Anchor Books, 1990, p. 413



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# Congenital Arteriovenous Communications and the Development of Two Types of Leaking Retinal Macroaneurysms

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Johan R. M. Cruysberg, M.D., and Albert L. Aandekerker, F.O.P.S.

We treated a patient with a rare combination of congenital arteriovenous communications and the development of leaking macroaneurysms of different types. Initially, leaking macroaneurysms developed in the shunt area of the arteriovenous communication; later, a preexistent fusiform macroaneurysm in the afferent arteriole of the congenital communication started leaking. Because exudates and fluid from the leaking macroaneurysms reached the fovea, laser treatment was performed to obliterate the macroaneurysms. We assume that after obliteration of the macroaneurysms with laser in the shunt area, the increase of hydrostatic pressure on the thin wall of the fusiform aneurysm of the afferent artery led to its leaking. We saw no signs of vascular occlusion after laser treatment.

**C**ONGENITAL ARTERIOVENOUS communications are rare developmental anomalies.<sup>1</sup> According to the study of Archer and associates,<sup>2</sup> these communications can be divided into three groups. The first group is characterized by the interposition of an arteriolar or abnormal capillary plexus between the major communicating vessels, generally localized to one quadrant of the retina. Most cases are asymptomatic. The second group comprises arteriovenous communications of large caliber, which may show evidence of stress and decompensation. The afferent arteries show beading and multiple fusiform dilatations of the walls. Areas of non-

perfusion are often present. The third group encompasses those arteriovenous malformations that are characterized by anastomosing channels of large caliber, widespread fluid leakage, and vascular occlusions that give rise to retinal complications leading to severe impairment of vision. The fundus findings in this group closely resemble some of those described by Wyburn-Mason<sup>3</sup> in 1943. Further possible complications of arteriovenous communications are run in intraretinal macular hemorrhage, retinal vein occlusion, neovascular glaucoma, and vitreous hemorrhage.<sup>4</sup>

Macroaneurysms are mostly isolated, acquired dilatations of retinal arteries with a strong association with hypertension and generalized atherosclerotic disease.<sup>5,6</sup> Most patients are women older than 60 years of age.<sup>6,7,8</sup> Isolated venous macroaneurysms have also been described with and without apparent venous obstruction.<sup>8,9,10</sup> Often the macroaneurysms are surrounded by retinal hemorrhage, exudates, macular edema, and occlusion of arterioles. Since macroaneurysms complicated by exudates and retinal edema in the macular area have a more damaging effect than those that are complicated only by hemorrhage, we treated these macroaneurysms with the dye laser.<sup>10</sup>

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## Case Report

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In 1986, an otherwise healthy 62-year-old woman was admitted to our institution because of a three-month history of impaired vision of the left eye. Visual acuity in this eye was counting fingers according to the referring ophthalmologist. On examination in our clinic, visual acuity had improved spontaneously to 20/30; visual acuity of the right eye was 20/25. Slit-lamp examination showed moderate nuclear

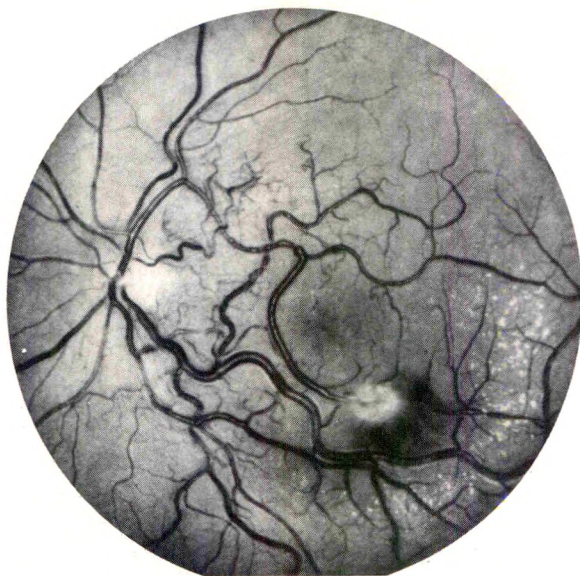
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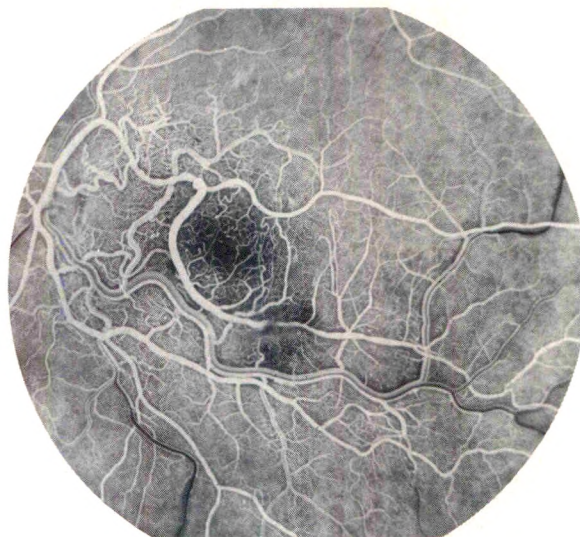
From the Institute of Ophthalmology, University of Nijmegen, the Netherlands.

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**Fig. 1** (Tilanus and associates). Left eye. Arteriovenous communications in the macular area and an occluded macroaneurysm inferotemporal to the macula with hard exudates.



**Fig. 2** (Tilanus and associates). Fluorescein angiogram in the arteriovenous phase with fusiform aneurysms of the afferent arteriole. There are no signs of leakage from the macroaneurysm.

lens changes in both eyes. Results of ophthalmoscopy of the right eye were normal. The fundus of the left eye showed arteriovenous shunts in the macular area with fusiform aneurysms of the afferent arteriole. There was an occluded macroaneurysm inferotemporal to the macula with hard exudates (Fig. 1). The fluorescein angiogram of the afferent arteriole with the fusiform aneurysms showed no more leakage from the macroaneurysm (Fig. 2). After several months all exudates resolved spontaneously. Visual acuity improved to 20/25 in the left eye.

In March 1990, the patient again had an impairment in vision, with visual acuity of 20/10 in the left eye. A new leaking macroaneurysm had developed between two pathologic communicating vessels (Fig. 3). The exudates extended into the macular area. Because of the central leakage, we decided to treat this macroaneurysm with dye laser at settings of 595 nm, 200  $\mu$ m, and 200 mW around and 500  $\mu$ m, 300 mW on this macroaneurysm. In the following months a considerable leakage remained, and the area was again treated with laser. After six months, one of the chronic fusiform aneurysms of the afferent arteriole began to leak (Fig. 4). This aneurysm was also treated with dye laser. At the most recent examination (October 1990), visual acuity was counting fingers in the left eye; exudates and edema were decreasing. The patient had no neurologic symptoms. A neuro-

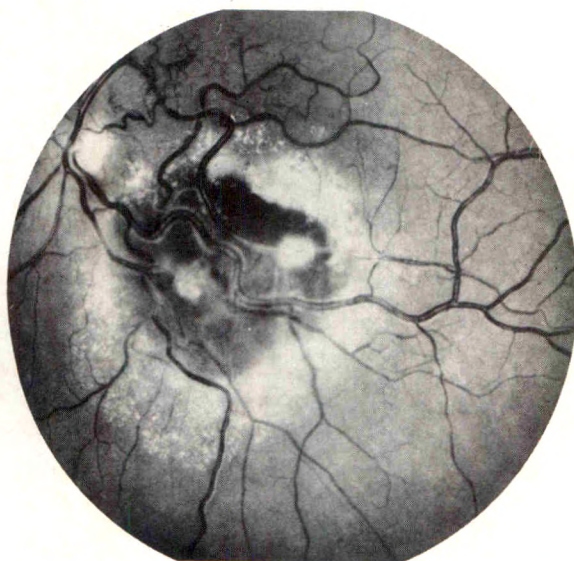
logic screening by computed tomography with and without contrast dye showed no signs of intracranial macroaneurysms. A cerebral angiogram was not performed.

## Discussion

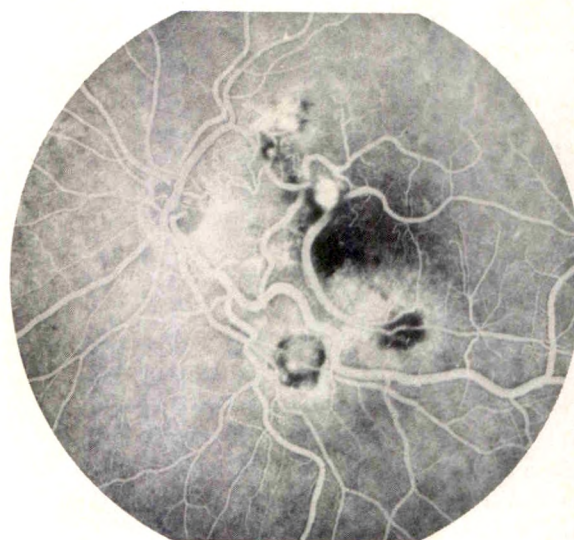
Arteriovenous communications of the retinal arteries are congenital malformations of the vascular tree. Most cases are unilateral. The presence or absence of a capillary system between the major communicating vessels, the size of the communication, the number of communications, and their location within the retina determine the extent, complexity, and possible complications.<sup>2</sup> Macroaneurysms of retinal arteries are acquired dilatations of the vascular wall. Diabetes mellitus, retinal vein occlusion, and subretinal neovascularization can play a role in the pathogenesis in addition to hypertension, advanced age, and generalized atherosclerotic disease.

Our patient had a rare combination of unilateral congenital arteriovenous communications and two macroaneurysms that developed in the shunt area between the inferotemporal vein and arteriole. One macroaneurysm closed spontaneously, and visual acuity improved as a result. The second macroaneurysm developed





**Fig. 3** (Tilanus and associates). Four years later, a new macroaneurysm developed between two pathologic communicating vessels.



**Fig. 4** (Tilanus and associates). Fluorescein angiogram showing some residual leakage from the treated macroaneurysm and new leakage from the preexistent fusiform aneurysm superior to the fovea.

four years later and again led to visual loss as a result of leakage of fluid and exudates. This macroaneurysm was treated with laser. Possibly because of altered vascular pressure in the preshunt area after laser treatment, the chronic fusiform macroaneurysm began leaking. Although macroaneurysms often close in their natural course, we treated the leaking macroaneurysms because of the damaging effect of chronic fluid and exudate accumulation in the macula. After laser treatment the macroaneurysms obliterated, without arterial obstructions. Thus, two types of leaking macroaneurysms were present, one in the shunt area between the inferotemporal vein and arteriole and a fusiform macroaneurysm typically seen with abnormal arteriovenous malformations.

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# Ultrastructural and Immunohistochemical Features of Coronal Adenomas

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We studied by electron microscopy three coronal adenomas discovered incidentally in eyes removed surgically. Tumor cells displayed prominent intercellular interdigitations with numerous desmosomes, mitochondria, abundant rough endoplasmic reticulum, and nuclei with membrane infoldings and a granular chromatin pattern. In these characteristics, the tumor cells were identical to nonpigmented ciliary epithelium of the ciliary processes. These growths contained abundant extracellular material, which showed a dimorphic pattern of complex reduplicated basal lamina and granular areas without structure. Immunohistochemical studies on formalin-fixed, paraffin-embedded coronal adenomas demonstrated type IV collagen and laminin in the extracellular material. These findings confirm that coronal adenomas develop from nonpigmented ciliary epithelium and that the extracellular material of these tumors contains components normally present in basement membranes.

**C**ORONAL ADENOMAS (Fuchs' adenoma, Fuchs' epithelioma, benign ciliary epithelioma) are small, age-related tumors of the ciliary processes.<sup>1,2</sup> Since the first description by Fuchs in 1883,<sup>3</sup> they have been studied thoroughly by light microscopy<sup>1,2,4-7</sup> and are characterized by

cords of benign, nonpigmented epithelial cells interspersed within abundant amorphous, eosinophilic extracellular material. On histologic and cytomorphologic grounds, coronal adenomas are believed to be growths of the nonpigmented ciliary epithelium. The acellular component of the tumor is strongly positive for periodic acid-Schiff stain, even the pretreatment by diastase, staining characteristics that are consistent with basement membrane.<sup>1,2</sup> Electron microscopic analysis of coronal adenomas has been attempted, but poor preservation of the tissue has precluded more than a cursory assessment of ultrastructural detail.<sup>1</sup>

Because of their peripheral retroiridial location and small size, coronal adenomas are almost always asymptomatic and are observed clinically only rarely. Thus, specimens for pathologic study are usually incidental discoveries in eyes removed at autopsy and are therefore inadequately preserved for ultrastructural analysis. We studied the ultrastructural features of three coronal adenomas observed in eyes removed surgically and immediately fixed for electron microscopic study. Additionally, we studied the immunohistochemical properties of the extracellular material in formalin-fixed, paraffin-embedded coronal adenomas.

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## Material and Methods

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Three eyes removed surgically were placed in fixative containing either 2% glutaraldehyde and 2% paraformaldehyde or 4% paraformaldehyde. All eyes were opened and examined with a dissecting microscope by one of us (R.Y.F.) according to methods described previously.<sup>8</sup> One eye was enucleated for a malignant melanoma involving the choroid and ciliary body; the coronal adenoma discovered upon opening the eye was remote from the melanoma. The remaining two eyes were part of orbital exenteration specimens removed for invasive

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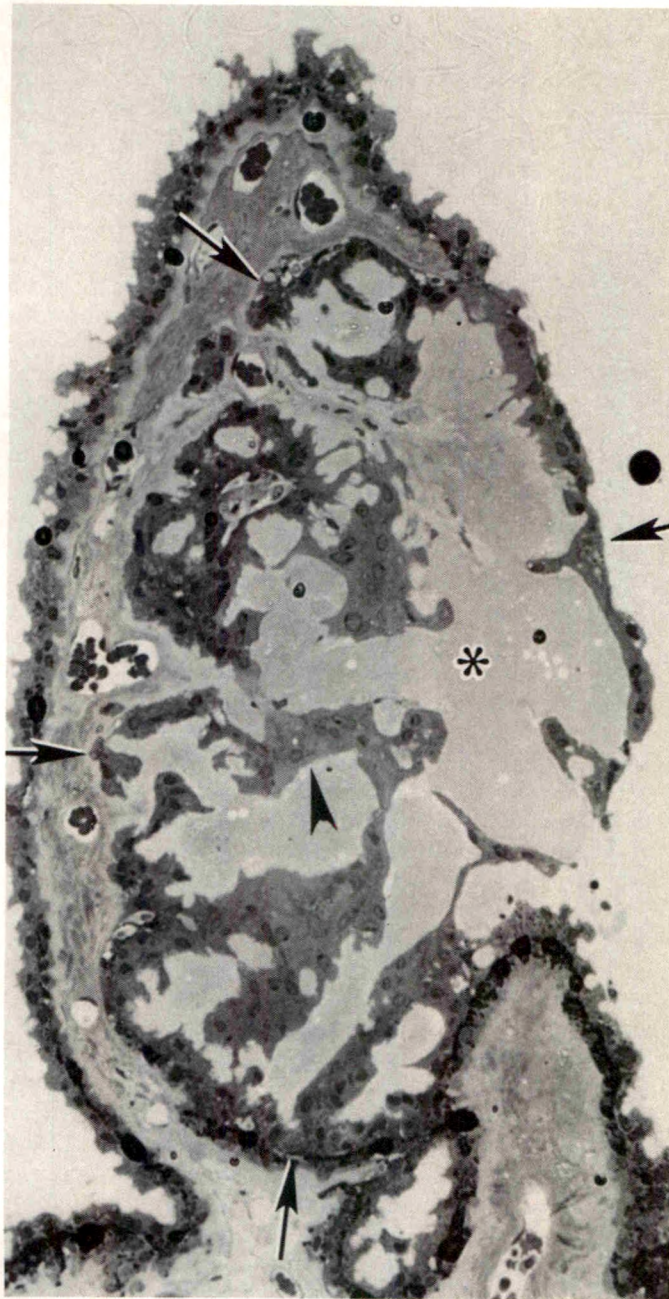


basal cell carcinoma and sebaceous carcinoma of the eyelids. In both cases coronal adenomas were the only significant intraocular pathologic findings.

The coronal adenomas were excised from the globes, postfixed in osmium tetroxide, and embedded in Araldite. Sections of 1- $\mu$ m thickness were prepared and stained with methylene blue. Ultrathin sections were then made, stained with uranyl acetate and lead citrate, and

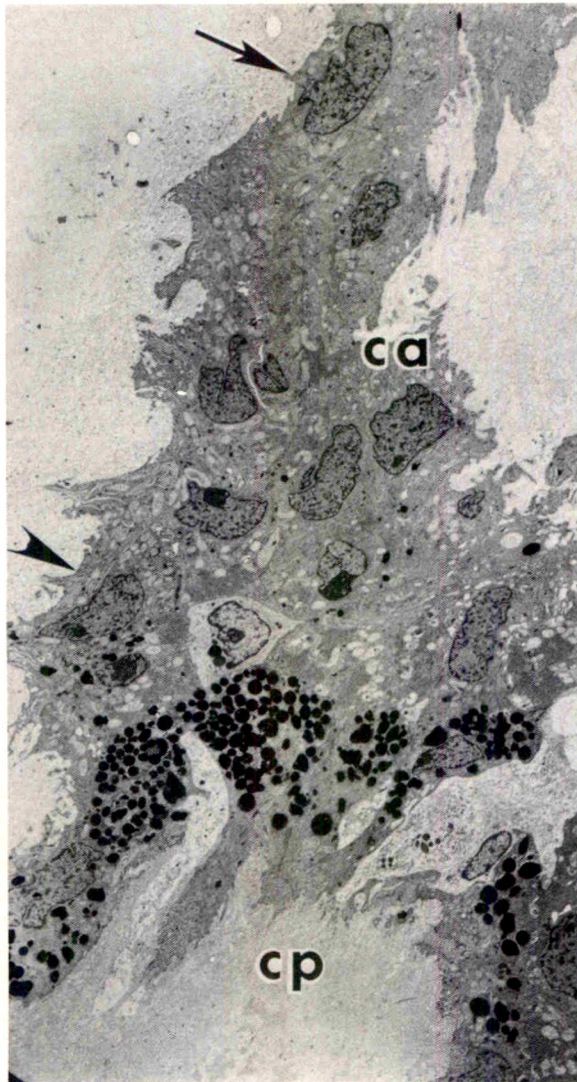
examined with a Siemens Elmiskop electron microscope.

Four eyes removed at autopsy, which also were found to contain coronal adenomas, were fixed in formalin and embedded in paraffin. Sections of 6- $\mu$ m thickness were cut, deparaffinized in xylene, pretreated with hydrogen peroxide and normal rabbit serum (swine serum for the laminin procedure) as a blocking agent, and allowed to react with commercially



**Fig. 1** (Brown, Glasgow, and Foos). A section of 1- $\mu$ m thickness shows a coronal adenoma (arrows) developing from the side of a ciliary process. Note the irregular nests and cords of nonpigmented ciliary epithelium (arrowhead) and abundant extracellular material (asterisk) (methylene blue,  $\times 40$ ).





**Fig. 2** (Brown, Glasgow, and Foos). At the juncture of the corneal adenoma (ca) with the ciliary process (cp), tumor cells (arrow) are contiguous with and indistinguishable from normal nonpigmented ciliary epithelium (arrowhead) ( $\times 1,700$ ).

prepared goat antisera to collagen types I through IV (Southern Biotechnology Associates, Inc., Birmingham, Alabama) and rabbit antilaminin (Polysciences, Inc., Warrington, Pennsylvania). Optimal results were obtained with an indirect peroxidase method for collagen types I and II, avidin-biotin complex method for collagen types III and IV, and peroxidase-antiperoxidase method for laminin. The chromagen substrate, 3-amino 9-ethylcarbazole, was applied in all methods. By light microscopy, reaction products were judged as

negative, weakly positive, or strongly positive. Appropriate positive and negative controls were performed.

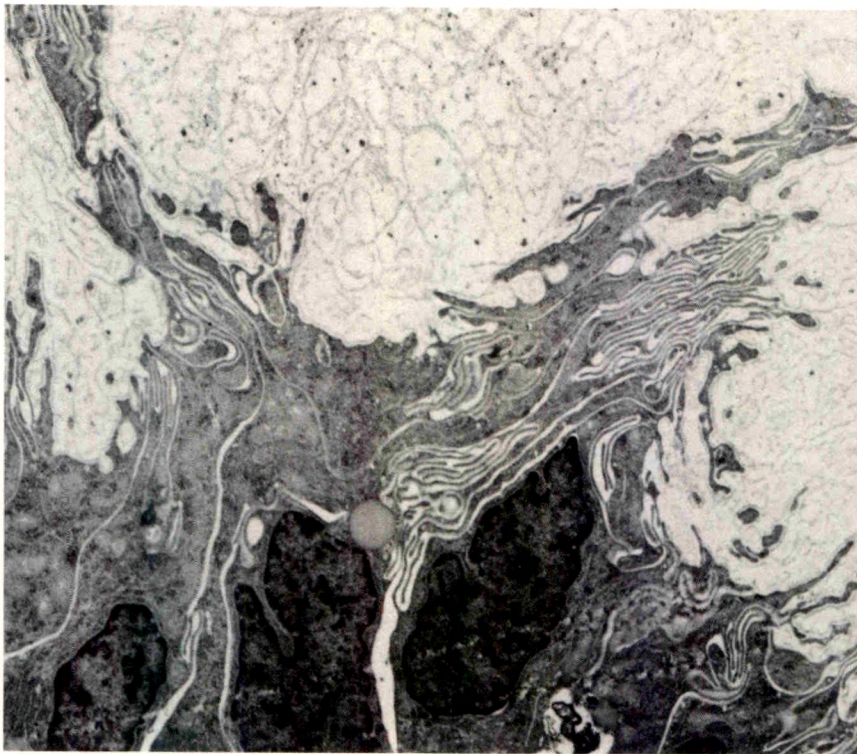
## Results

**Electron microscopic findings**—In all cases studied, the corneal adenomas exhibited identical ultrastructural characteristics. Cells were arranged in cords and fingerlike projections, separated by an extracellular material that demonstrated a biphasic pattern (Fig. 1). At the periphery of the tumor the cells were continuous with the nonpigmented epithelium of the ciliary process (Fig. 2). A discontinuous monolayer of pigmented epithelial cells separated the tumor from the stroma of the ciliary process. At this interface occasional tumor cells contained small numbers of melanosomes, a feature also observed in nonpigmented ciliary epithelium elsewhere in the ciliary processes. Tumor cells demonstrated elaborate intercellular interdigitations (Fig. 3). Specialized cell-cell attachments in the forms of desmosomes and gap junctions were numerous (Fig. 4); however, no tight junctions were seen. The free surfaces of the cells were more variable in appearance, ranging from relatively smooth to markedly convoluted. Multiple layers of basal laminae lined the free surfaces of all tumor cells, whether abutting the extracellular material or the posterior chamber.

The cytoplasm of the tumor cells contained abundant rough endoplasmic reticulum, primarily in a perinuclear location. Mitochondria were also present but to a lesser degree than in normal nonpigmented ciliary epithelium. Occasional clusters of secondary lysosomes containing variably electron-dense material were present. Golgi apparatus and smooth endoplasmic reticulum were sparse. Centrioles exhibiting a 9+0 arrangement of microtubules (nine peripheral microtubular complexes without any central microtubules) were observed infrequently. Tumor cell nuclei were located centrally and ranged from 7 to 10  $\mu\text{m}$  in diameter. The nuclear outlines were irregular, with numerous infoldings. Some nuclei contained single, peripherally placed nucleoli. The chromatin pattern was heterogeneous but generally condensed along the nuclear membrane. No mitotic figures were observed.

The extracellular material exhibited two pat-





**Fig. 3** (Brown, Glasgow, and Foos). Complex intercellular cytoplasmic membrane interdigitations are characteristic as well as fingerlike projections into the extracellular material ( $\times 9,240$ ).

terns (Fig. 5). Adjacent to the tumor cells there was a multilaminar matrix identical to the basal lamina of normal nonpigmented ciliary epithelium remote from the tumor. Deeper within the acellular spaces, however, the material became finely granular and without structure. Within the granular material were rounded, electron-lucent spaces, as well as profiles of vesicular bodies interpreted as degenerated cytoplasmic organelles. Rarely, isolated thin fibrils were noted.

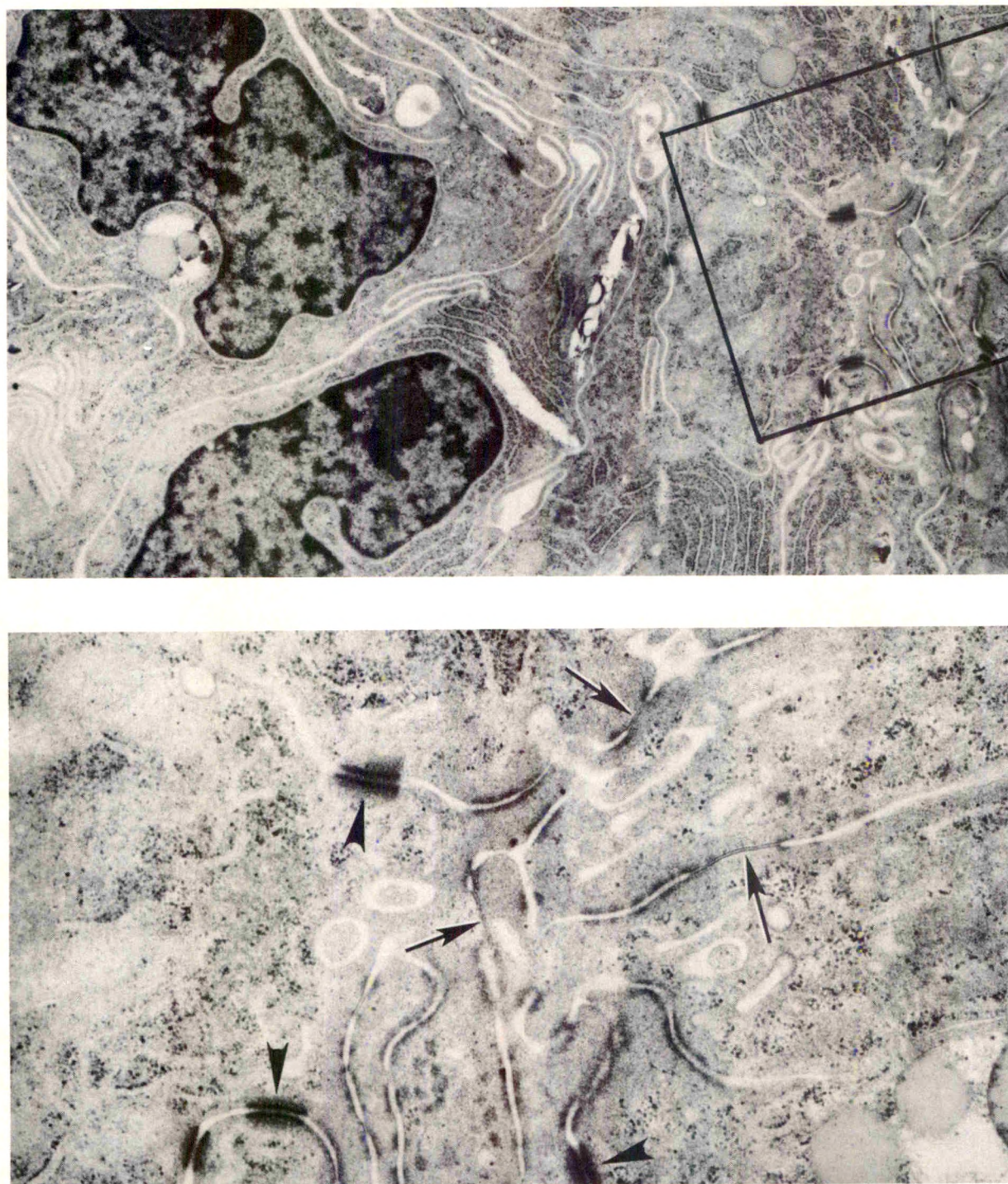
**Immunohistochemical findings**—The immunohistochemical reactions of the extracellular matrix were uniform in all cases examined. No reaction product was observed with antisera to collagen types II and III. Staining for type I collagen was weakly and only focally positive in areas adjacent to tumor cells. Immunohistochemical staining for type IV collagen produced the strongest reaction, which was more pronounced adjacent to the tumor cells but also present deeper within the extracellular material (Fig. 6). Antisera to laminin stained bordering the tumor cells.

## Discussion

Coronal adenomas have been recognized for more than a century<sup>3</sup> but only in the last two decades have they been more fully characterized.<sup>1,2</sup> Controversy exists regarding their pathogenesis and neoplastic potential. Some investigators regard these tumors as age-related hyperplastic proliferations of nonpigmented ciliary epithelium,<sup>9-11</sup> but the only proposed cause for such a localized tissue reaction is that senile amyloid deposition within capillary walls and stroma of ciliary processes incites an epithelial proliferation.<sup>6</sup> Other authors believe that these tumors are benign neoplasms.<sup>1-3,12</sup> Ultimately this question may only be resolved at the molecular level by determination of clonality of the genetic makeup of the tumor cells.

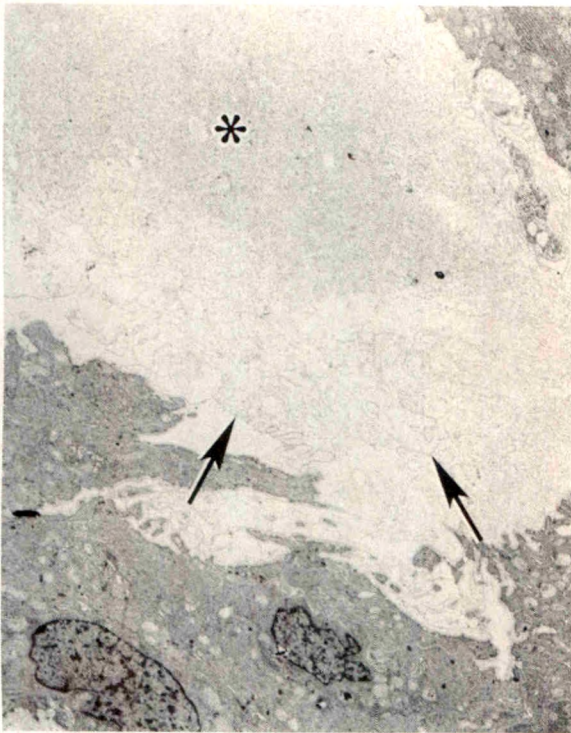
There is general agreement that coronal adenomas are derived from nonpigmented ciliary epithelium, based on gross and light microscopic findings.<sup>1,2,4-7</sup> However, at least two pigmented coronal adenomas have been docu-





**Fig. 4** (Brown, Glasgow, and Foos). Top, Nuclei are irregularly indented, and the cytoplasm is rich in rough endoplasmic reticulum ( $\times 23,240$ ). Bottom, Higher magnification of the outlined area demonstrates numerous intercellular desmosomes (arrowheads) and gap junctions (arrows) ( $\times 56,000$ ).

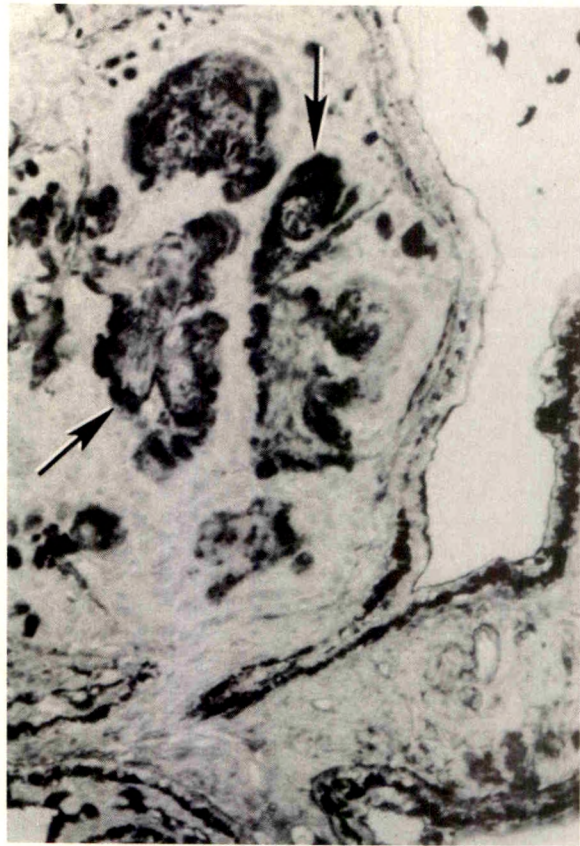




**Fig. 5** (Brown, Glasgow, and Foos). Extracellular material demonstrates multiplication of basal laminae (arrows) bordering tumor cells, merging into granular and vacuolar regions (asterisk) deeper within the extracellular substance ( $\times 2,350$ ).

mented.<sup>2,13</sup> Since these lesions usually are discovered incidentally in eyes removed after death, proper preservation for ultrastructural examination is not often achieved. Electron microscopic examination of coronal adenomas has been reported.<sup>1,6</sup> Iliff and Green<sup>1</sup> made some general observations of the ultrastructural features of two coronal adenomas in postmortem specimens, but poor preservation precluded detailed examination. Gartner<sup>6</sup> properly processed for electron microscopic study one coronal adenoma in a surgically enucleated eye but limited his description and illustrations primarily to the presence of amyloid within the ciliary process stroma adjacent to the tumor. We did not identify amyloid histochemically or ultrastructurally either within the ciliary process stroma or the extracellular material of the coronal adenoma.

Our findings substantiate the belief that coronal adenomas develop from nonpigmented ciliary epithelium. At the ultrastructural level coronal adenomas are contiguous with the monolayer of nonpigmented ciliary epithelium lining the inner surface of the ciliary process from which they originate. The presence of



**Fig. 6** (Brown, Glasgow, and Foos). Immunohistochemical reaction product for type IV collagen is present within the extracellular material (arrows) ( $\times 40$ ).

numerous complex intercellular interdigitations, as seen in the three cases examined, is characteristic of normal nonpigmented ciliary epithelium of the pars plicata.<sup>14</sup> The other distinguishing feature of nonpigmented ciliary epithelium, the presence of zonula occludens between apices of adjacent cells,<sup>14</sup> was not observed between tumor cells in the preparations we examined. Absence of zonula occludens indicates a deficiency of a specific specialized cell feature and supports the theory that these tumors are indeed neoplasms and not hyperplastic proliferations of fully mature epithelial cells. Other specialized intercellular connections, such as desmosomes and gap junctions, are identified within the tumor.

The limited growth potential of these proliferations may pertain more to cellular adaptation to decreased metabolic supply than to lack of neoplastic transformation. Coronal adenomas have no appreciable fibrovascular interstitium from which to derive nutrients or a stable supporting framework on which to proliferate. In-



deed, the cells more remote from the ciliary process contain fewer cytoplasmic organelles and a simpler, more rounded cell outline, which suggest a reduced cellular metabolic rate.

The prominent extracellular component of these tumors is in part identical to the multiple layers of basal laminae exhibited by normal nonpigmented ciliary epithelium. In particular, the zone immediately adjacent to tumor cells is unmistakably basal lamina by ultrastructural and immunohistochemical evaluation. At a greater distance from the tumor cells, however, the extracellular material exhibits a granular, amorphous appearance with occasional round, electron-lucent spaces. Rarely, degenerated cellular material is found within both the multilaminar and the granular portions. The nature of the central granular material is unclear. It may represent an accumulation of some normal molecular component (or components) of basement membrane, or it may represent sequestration of degenerated basal lamina. The immunohistochemical staining patterns are not conclusive with regard to the central granular material, which suggests that the material is degenerated and devoid of antigenic sites necessary for reaction with the antisera tested or that appropriate antisera that would identify the material have not been used.

The cellular ultrastructural findings in corneal adenomas are in essence the same as those reported by Patrinely and associates,<sup>9</sup> who described a hamartomatous adenoma of the nonpigmented ciliary epithelium. Ultrastructurally, however, they found numerous fine collagen fibrils interspersed within the reduplicated basal laminae lining the tumor cells. This finding, as well as the positive histochemical staining for hyaluronidase-sensitive Alcian blue within the stroma of the tumor, indicated the presence, and presumably the production, of vitreous by the tumor. No ultrastructural or histochemical patterns characteristic of vitreous were detected in the corneal adenomas we examined.

Although nonpigmented epithelium covers both the pars plana and the pars plicata of the ciliary body, corneal adenomas are found strictly in the pars plicata. Structural and biochemical differences have been noted between the epithelium lining the ciliary processes and the pars plana.<sup>14</sup> Histologically, localized proliferations of pigmented and nonpigmented ciliary epithelium of the pars plana are common findings in adult eyes<sup>15</sup> and most likely are responses to tractional forces from vitreous

fibrils and zonular fibers within the vitreous base. Corollary thinking might suggest that zonular traction induces similar proliferations along the sides and valleys of ciliary processes, which supports the contention that corneal adenomas are reactive hyperplasias rather than true adenomas. Corneal adenomas, however, also occur along the apices and the rounded anterior projections of the ciliary processes, sites normally lacking in zonular fiber attachments.

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# Identifying Progression of Subclinical Keratoconus by Serial Topography Analysis

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Leo J. Maguire, M.D., and Jonathan C. Lowry, M.D.

We performed serial slit-lamp examinations and topography analysis on a patient whose initial topographic map suggested a diagnosis of keratoconus to us but which others interpreted as normal topography. Topography analysis documented cone progression during a two-year period. The initial map showed a cone apex power of 44.5 diopters located 2.1 mm inferior to the vertex normal. An oblong-shaped area of maximum power was surrounded by concentric bands of lower power. Corneal surface power ranged from 41.5 to 44.5 diopters. Two years later cone apex power increased to 51.0 diopters, and the patient developed a Fleischer's ring, Vogt's striae, and mild visual aberration. Our findings suggest the use of topography analysis systems in documenting subclinical cone progression. Topography systems may be a useful tool in the study of the true incidence and natural progression of subclinical keratoconus.

**T**HE USE OF TOPOGRAPHY ANALYSIS SYSTEMS to detect subclinical keratoconus is gaining acceptance,<sup>1-3</sup> but controversy exists regarding the minimum topographic criteria for diagnosis of the earliest stages of subclinical keratoconus.<sup>2,4,5</sup> The distinction between normal topography and early keratoconus will be clearer when maps with patterns suggestive of early subclinical keratoconus are documented to show progression to clinically obvious disease. We studied one such patient.

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## Patients and Methods

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We performed serial slit-lamp examinations and topographic analysis (Corneal Modeling System, Computed Anatomy, New York, New York) on the left eye of a patient we believed to have early subclinical keratoconus but which others suggested may be normal.

The first topography map in the series was described in the study of Maguire and Bourne<sup>1</sup> on the topography of early keratoconus. That map showed a cone apex power of 44.5 diopters located 2.1 mm inferior to the vertex normal. This area of maximum corneal power was surrounded by concentric rings of progressively lower power. Corneal surface power ranged from 41.5 to 44.5 diopters.

The patient had clinically obvious keratoconus in the fellow eye but no biomicroscopic evidence of keratoconus (stromal thinning, Fleischer's ring, Vogt's striae, and anterior stromal scarring<sup>6</sup>) in the eye being studied. The patient had no visual complaints in the right eye at the time of the initial topographic analysis. There was no history of contact lens wear. Uncorrected visual acuity was 20/20.

Topography analysis was performed at two- to three-month intervals during the next two years with previously described methods.<sup>1</sup> The patient was examined carefully for biomicroscopic evidence of keratoconus (Fleischer's ring, Vogt's striae, anterior stromal scarring, and stromal thinning).

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## Results

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A topography map was obtained six months after the initial examination (Fig. 1). Power at the cone apex increased to more than 47.0 diopters, and the range of power on the corneal surface increased from the map reported in the earlier article.<sup>1</sup> Topography obtained 15 months

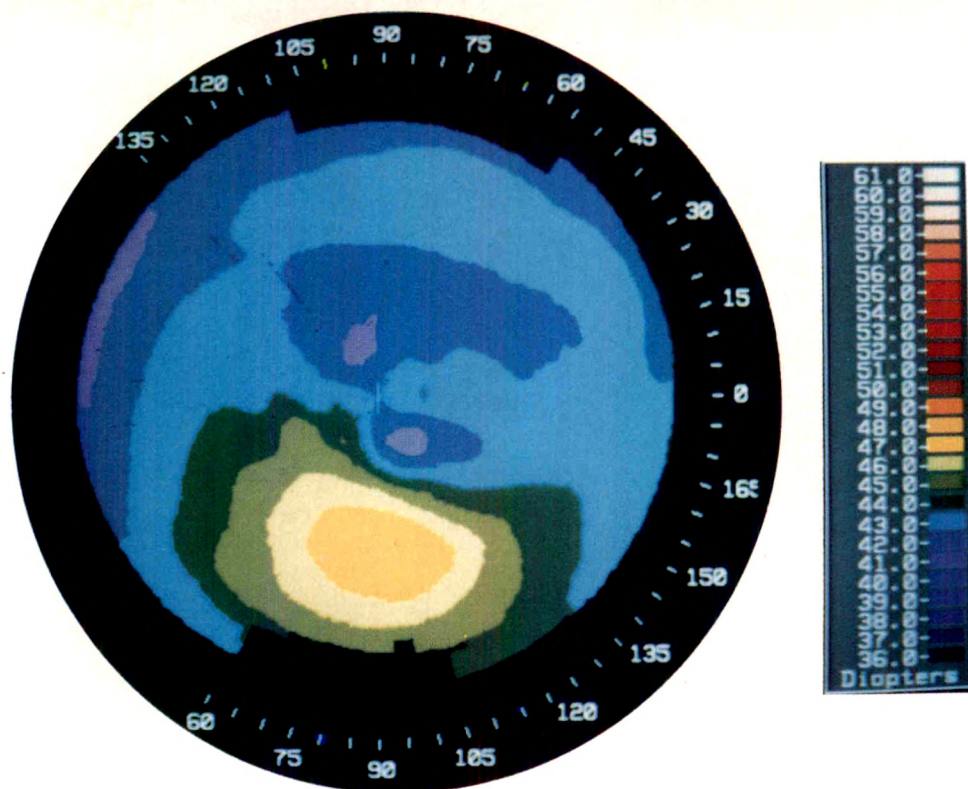
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Accepted for publication March 20, 1991.

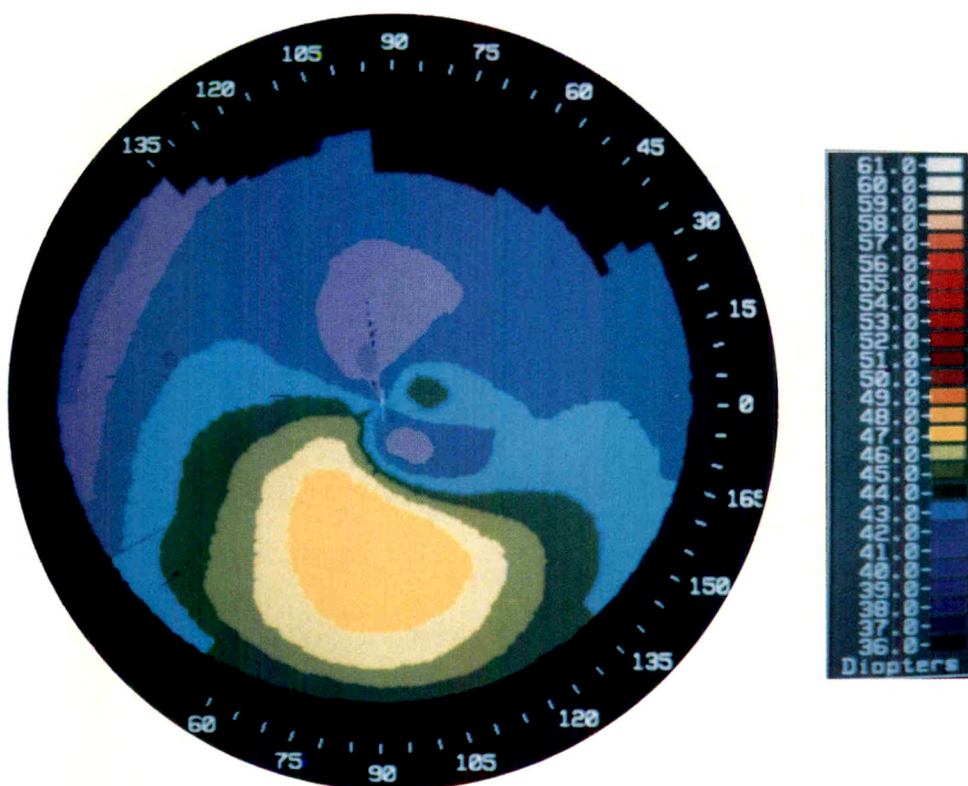
From the Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota. This study was supported in part by Research to Prevent Blindness, Inc., National Institutes of Health grant EY03039, and the Mayo Foundation, Rochester, Minnesota.

Reprint requests to Leo J. Maguire, M.D., Department of Ophthalmology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.





**Fig. 1** (Maguire and Lowry). Computer-generated color contour map of the left eye six months after the initial examination showed a cone with a maximum power of 44.5 diopters. Each color represents a 1.0-diopter range of surface power. Colors in the blue spectra represent lower powers, and colors closer to the red spectra represent higher powers. Figures 2 through 4 use the same scale. The range extends from 41.0 diopters to greater than 47.0 diopters at the cone apex in this figure.



**Fig. 2** (Maguire and Lowry). Contour map of the same eye shown in Figure 1 nine months after the examination. A slight increase in power is observed in the area surrounding the cone apex.



after the initial examination showed the area of the cone had increased (Fig. 2). Topography obtained 18 months after the initial examination showed continued cone progression (Fig. 3). Power at the cone apex increased to 49.0 diopters. Vogt's striae and an early Fleischer's ring were detected for the first time. Topography obtained 20 months after the initial examination showed continued cone progression with a cone apex power of 51.0 diopters and cone area enlargement (Fig. 4). The patient reported visual aberration for the first time. Uncorrected visual acuity remained at 20/20.

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### Discussion

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The findings in our patient demonstrate the method that must be used to differentiate between normal corneal topography and early subclinical keratoconus. This patient initially had a pattern of power distribution that suggested a mild inferiorly displaced cone to us but which others suggested might be normal.<sup>4,5</sup> At that time we stated that the only way to settle the controversy was to obtain serial topographic analysis on this and other patients with topographic findings suggestive of keratoconus and to demonstrate progression to clinically obvious disease. By documenting progression from early subclinical keratoconus (apex power of 45.0 diopters surrounded by concentric bands of increasingly lower power) to clinically apparent disease, this case demonstrates the efficacy<sup>3</sup> of serial topography analysis in determining that a particular topographic pattern suggestive of early subclinical keratoconus is keratoconus.

We know little about the early stages of keratoconus development. The patient with keratoconus putatively begins life with a normal cornea. Subclinical keratoconus develops and in some cases progresses to clinically apparent disease.<sup>7</sup> A number of investigators suggested that information derived from keratoscope-based topography systems be used to develop numeric descriptors that can differentiate between normal topography and subclinical keratoconus.<sup>4,5</sup> Anyone developing such indices must recognize that keratoconus may take many shapes, including oval and nipple cones, which may be variously located relative to the center of the cornea.<sup>1-3,6,7</sup>

Rabinowitz, Garbus, and McDonnell<sup>2</sup> performed topography analysis on 28 family mem-

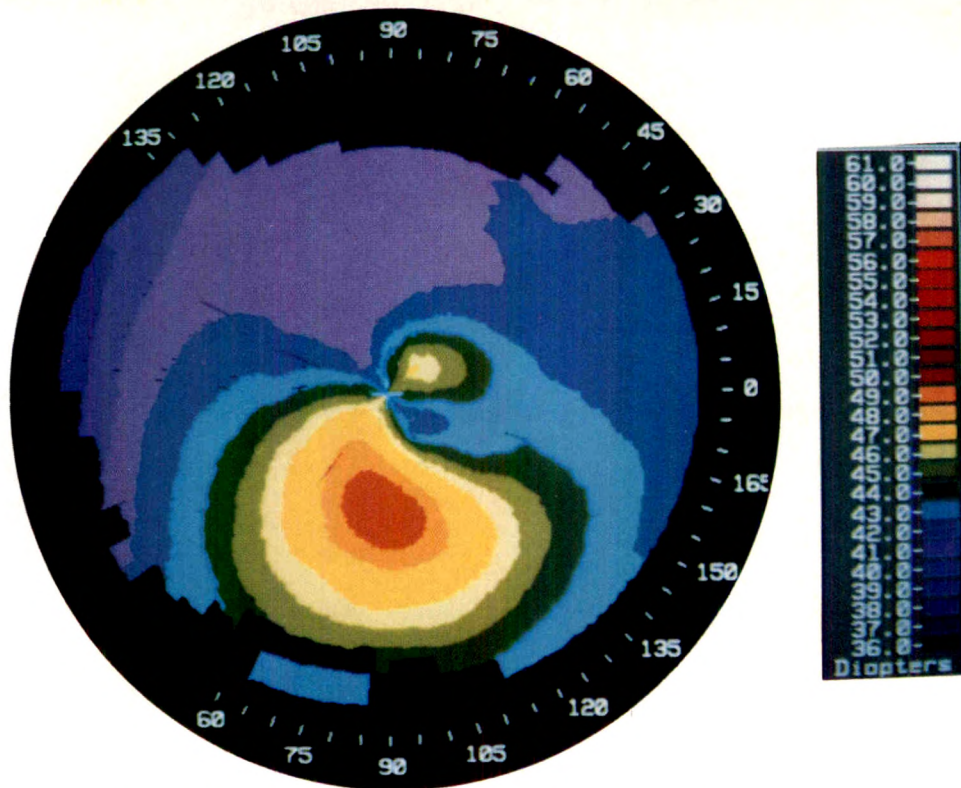
bers of five patients with keratoconus. Half of the subjects showed at least one of five topographic abnormalities not observed in the control group. The authors considered these abnormalities to be similar to, but less severe than, those found in the patients with keratoconus. They developed indices based on topography analysis that differentiated between the control group and the experimental group, but they could not determine with certainty that the patterns observed represented subclinical keratoconus.

The only way to prove that a particular abnormal pattern of topography is consistent with a diagnosis of subclinical keratoconus is to perform serial topography analysis and document progression to clinically obvious disease. Once that is done and larger studies are performed on the normal population,<sup>8,9</sup> one can begin to develop numeric descriptors that may differentiate between normal subjects, various manifestations of subclinical keratoconus, and other types of abnormal topography. If the task follows the path of most clinical endeavors, a number of false starts will precede the development of objective topographic measures with the sensitivity and specificity to be clinically useful.

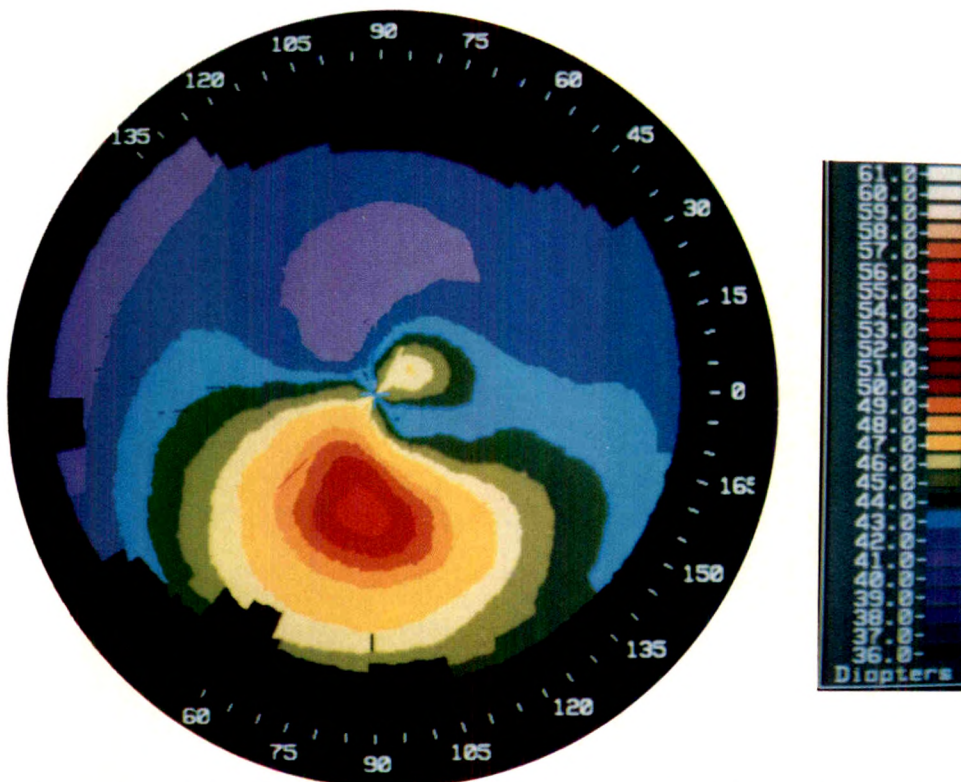
There are many compelling reasons to perform this work. A prospective population-based study using serial topography analysis could elucidate the true incidence of unilateral keratoconus and document patterns and rates of progression.<sup>7</sup> Patients identified as having subclinical keratoconus could be excluded from keratorefractive procedures.<sup>1</sup> The study of Rabinowitz, Garbus, and McDonnell<sup>2</sup> emphasizes its importance in understanding the role of heredity in keratoconus. Finally, the identification of topography patterns consistent with subclinical keratoconus may improve our understanding of the relation of contact lens wear to keratoconus.<sup>10,11</sup>

Macsai, Varley, and Krachmer<sup>10</sup> suggested that contact lens wear can cause a specific type of keratoconus characterized by central cone position, flatter keratometry readings, and older age at the time of diagnosis. An alternative explanation is that the patients have subclinical central keratoconus at the time of initial lens fitting and undergo a natural progression of their disease. The finding that a steep central corneal topography pattern is one of the abnormalities found in asymptomatic family members of patients with keratoconus lends credence to this notion.<sup>2</sup> Documentation of





**Fig. 3** (Maguire and Lowry). Contour map of the same eye shown in Figure 1 one year after the examination. Topographic progression is evident with the cone apex increasing to 49.0 diopters. Vogt's striae and portions of a Fleischer's ring are apparent for the first time.



**Fig. 4** (Maguire and Lowry). Contour map of the same eye shown in Figure 1 14 months after the examination. Cone apex power is more than 51.0 diopters. The patient has visual acuity of 20/20 without correction but has visual aberration for the first time.



progression to keratoconus in patients with this topographic pattern who do not wear contact lenses could change the tone of debate between those who support and refute the hypothesis of Macsai, Varley, and Krachmer.<sup>10</sup>

Our study shows that serial topography analysis can document stages of progression of subclinical keratoconus and identify a topographic pattern consistent with the diagnosis. We hope the method will be incorporated and validated in prospective studies of the natural course and heredity of the condition.

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### OPHTHALMIC MINIATURE

"They are taking hostages now—from all the villages where they think you've been. And if people don't tell. . . somebody is shot. . . and then they take another hostage. It happened in Concepcion."

"Concepcion?" One of his lids began to twitch, up and down, up and down: in such trivial ways the body expresses anxiety, horror, or despair.

Graham Greene, *The Power and the Glory*  
New York, Viking Penguin, 1990, p. 81



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## Ocular Infections Associated With *Comamonas acidovorans*

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Karl G. Stonecipher, M.D., Harold G. Jensen, Ph.D., Peter R. Kastl, M.D.,  
Alan Faulkner, M.D., and J. James Rowsey, M.D.

*Comamonas acidovorans* (*Pseudomonas acidovorans*) is a ubiquitous gram-negative rod. Although generally considered nonpathogenic, we found *C. acidovorans* to be associated with six cases of ocular infections. The organism was the only isolate in three cases, whereas an association of other organisms was present in three cases. The multiple resistance patterns of these strains to antibiotic susceptibility testing emphasizes the need for culturing ocular infections. We recommend the identification and susceptibility testing of all ocular gram-negative rod isolates.

*COMAMONAS ACIDOVORANS* (*Pseudomonas acidovorans*) is a ubiquitous gram-negative rod found in soil and water.<sup>1</sup> Although generally considered nonpathogenic, it has been isolated from sputum, urine, cerebrospinal fluid, and the pharynx.<sup>2</sup> *Comamonas acidovorans* has been implicated as the etiologic agent for nosocomial bacteremia,<sup>3</sup> endocarditis,<sup>4</sup> and otitis.<sup>5</sup> Brinser and Torczynski<sup>6</sup> reported *C. acidovorans* as a primary pathogen in human ocular disease. After review of our microbiologic files, we found six cases of ocular infection associated with this rare ophthalmic pathogen. Four of these cases were associated with contact lens wear, of which one developed keratitis, one blepharitis, and two were contact lens contaminants associated with *Acanthamoeba* keratitis. *Comamonas acidovorans* was also isolated from two noncontact lens wearers; one patient had

conjunctivitis and one had blepharitis. In each of these cases, the organism was found to have multiple antibiotic resistances. Except for the two cases of *Acanthamoeba*, the patients responded clinically to the appropriate antibiotics selected by susceptibility testing.

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### Case Reports

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#### Case 1

A 48-year-old woman had photophobia, redness, and tearing in the left eye for approximately 24 hours. The patient wore extended soft contact lenses and had removed the lenses the night before this manifestation; however, she still reported a foreign body sensation the next day. Corrected visual acuity was R.E.: 20/20 and L.E.: 20/20-1. Slit-lamp biomicroscopy showed an irregular, intact epithelium with 2 × 1-mm midperipheral area of stromal infiltrate at the 5 o'clock meridian. Additionally, there was an associated mild cell and flare in the anterior chamber and moderate injection of the conjunctiva of the left eye. Cultures were obtained from the cornea and contact lens. The patient was given fortified gentamicin sulfate (14 mg/ml) every hour while awake, bacitracin ophthalmic ointment two times per day, and 0.25% scopolamine hydrobromide two times per day in the left eye.

The Gram stain of the specimen obtained from the cornea disclosed no organisms. Cultures of the cornea and contact lens disclosed growth of *C. acidovorans*, which was resistant to ampicillin, cefazolin, and gentamicin sulfate. Upon evaluation of the sensitivities, tobramycin appeared to be the drug of choice, and the patient was administered this regimen every hour while awake. The gentamicin sulfate was discontinued. The tobramycin was tapered over a one-month period with resolution of the infectious process leaving a small stromal scar in the left eye.

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**Case 2**

A 57-year-old white woman had a history of chronic infection of the left eye for several months. On examination, visual acuity was R.E.: 20/20 and L.E.: 20/25. Slit-lamp examination showed a follicular conjunctivitis with a moderate amount of mucopurulent discharge in the cul-de-sac. The cornea was clear and did not stain with fluorescein. The anterior chamber was deep and quiet. Routine cultures of the eyelids and conjunctiva disclosed growth of *C. acidovorans*. The patient was administered a regimen of prednisolone acetate eyedrops with an associated resolution of the infection by the time final sensitivity reports were available.

**Case 3**

A 76-year-old white woman had a history of chronic blepharitis and meibomitis unresponsive to eyelid hygiene and warm compresses. Initial visual acuity was R.E.: 20/40+2 and L.E.: hand motions. Reduced visual acuity in the left eye was secondary to chronic glaucomatous changes. Eyelid and conjunctival cultures of both eyes disclosed no growth on the eyelid and conjunctiva of the left eye but growth of *C. acidovorans* in the right eye. The patient was given oral doxycycline and topical erythromycin. Based on final sensitivity reports, the regimen was changed to polymyxin B sulfate, and eyelid scrubs and oral doxycycline were continued. Repeat cultures two months after the initial manifestation were negative.

**Case 4**

A 16-year-old girl who wore daily-wear contact lenses had irritated and swollen eyelids associated with burning after inserting her contact lenses earlier. Best-corrected visual acuity was 20/25 in both eyes. Results of slit-lamp examination were normal except for moderate papillary changes of the right upper eyelid. Cultures of the eyelids and conjunctiva grew *Acinetobacter calcoaceticus* and *C. acidovorans*. She was instructed to discard her current contact lens case. Both organisms were sensitive to gentamicin sulfate, and the patient's clinical symptoms resolved without complications.

**Case 5**

A 32-year-old white man was referred to the Cornea Service with the diagnosis of possible *Acanthamoeba* keratitis. He had worn daily-wear soft contact lenses for 12 years. Visual acuity was R.E.: 20/20 and L.E.: 20/50+. He had stopped his daily-wear soft contact lenses

about one month before the initial manifestation. The patient used salt tablets for his saline solution. On examination, he had marked photophobia and significant tearing with mucoid discharge of both eyes. The right eyelids showed trace swelling, and the left eyelids showed mild to moderate swelling. There was significant epiphora of the left eye, much greater than the right eye. Both eyes had injection of the bulbar conjunctiva. The cornea was clear in the right eye without evidence of fluorescein staining. The anterior chamber in the right eye was deep and quiet without any signs of inflammation. The cornea of the left eye was remarkable for diffuse, spotty, ring infiltrates for 360 degrees. There also appeared to be some superior perineural infiltrates at the 11:30 and 5:00 o'clock positions. The ring infiltrate was also noted to stain slightly with fluorescein. The anterior chamber was deep and quiet. Cultures of the eyelid and conjunctiva of the left eye showed no growth. *Bacillus cereus* was isolated from the eyelid and conjunctiva of the right eye. Cultures of the contact lenses from both eyes showed confluent growth of *B. cereus*, *C. acidovorans*, and *Flavobacterium* species. *Acanthamoeba* was isolated from both of the contact lens specimens. The patient was given and responded well to propamidine, gramicidin, and scopolamine hydrobromide. Visual acuity after 120 days of follow-up was R.E.: 20/20+3 and L.E.: 20/20. Slit-lamp examination still showed ring scarring in the left eye but otherwise was unremarkable.

**Case 6**

A 26-year-old white woman was examined elsewhere for a history of extended-wear contact lens use. Specimens were sent to the Dean A. McGee Eye Institute Ocular Microbiology Laboratory for evaluation. Corneal biopsy taken at the time of initial manifestation disclosed focal areas with small cystlike organisms that were double walled with a central core compatible with *Acanthamoeba*. Cultures of the contact lens case, saline bottle, and distilled water were positive for growth of *C. acidovorans*. *Acanthamoeba* was isolated from the contact lens case and saline solutions as well as from the distilled water used to make these solutions.

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**Results**

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Ocular *C. acidovorans* isolates were evaluated at two centers. One isolate was evaluated at the







involved in the other three patients, the role of *C. acidovorans* in the infections can only be speculative. It certainly could have had an additive effect of irritation along with *Acinetobacter* on the eyelids and conjunctiva in one patient (Case 4). *Comamonas acidovorans* may not have had a direct effect on the two patients with *Acanthamoeba* keratitis (Cases 5 and 6), but these gram-negative rods may have been indirectly involved by acting as a food source for maintenance of the amoeba in both the distilled water and the contact lens solutions (unpublished data).

The susceptibility patterns of our *C. acidovorans* isolates seem to include a more prevalent and varied resistance pattern than those strains reported previously.<sup>4-6</sup> Our isolates were not all susceptible to any single antibiotic, and two isolates (both involving *Acanthamoeba* keratitis) were resistant to all antibiotics tested. Our data indicate that cefoxitin and perhaps tetracycline would be the most effective antibiotics for therapy for this particular nonfermenting gram-negative rod. The aminoglycosides that are commonly used for *Pseudomonas* infections would generally be ineffective.

Although *C. acidovorans* is probably of low pathogenicity and ocular infection is rare, its presence in any type of ocular infection would certainly warrant susceptibility testing. Knowledge of this organism's multiple resistance to antibiotics, especially the aminoglycosides, would require careful monitoring of the infection with diligent patient follow-up.

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## Diode Laser Compared With Argon Laser for Trabeculoplasty

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Rosario Brancato, M.D., Roberto Carassa, M.D., and Giuseppe Trabucchi, M.D.

A randomized prospective study on two groups of ten patients compared the efficacy of diode laser and argon laser trabeculoplasty. In the diode laser group the intraocular pressure was  $23.0 \pm 3.97$  mm Hg before the treatment,  $20.2 \pm 4.49$  mm Hg at two hours,  $16.3 \pm 3.13$  at six months, and  $16.9 \pm 2.80$  mm Hg at one year. The differences from baseline were statistically significant at six months ( $P = .0001$ ) and at one year ( $P = .0001$ ) but not at two hours. In the argon laser group the intraocular pressure was  $23.4 \pm 3.6$  mm Hg before the treatment,  $22.7 \pm 4.35$  mm Hg at two hours, and  $17.6 \pm 4.53$  mm Hg at six months. One patient had uncontrolled mean high intraocular pressure and underwent surgery. In the nine patients who completed the study the intraocular pressure at one year was  $16.7 \pm 3.00$  mm Hg. The differences from baseline were significant at six months ( $N = 10$ ;  $P = .0001$ ) and 12 months ( $N = 9$ ;  $P = .0001$ ) but not at two hours. Differences between the two groups were not significant at two hours, six months, and one year. Laser trabeculoplasty may be effectively with a diode laser.

SINCE THE PILOT STUDY by Wise and Witter,<sup>1</sup> argon laser trabeculoplasty has become an effective means for lowering intraocular pressure in primary and secondary glaucomas. Argon blue-green (488.0 to 514.5 nm) is usually employed as the source of laser energy. The efficacy of this treatment has also been investigated at different wavelengths such as with the monochromatic argon laser (514.5 nm),<sup>2</sup> krypton laser,<sup>3,4</sup> or Nd:YAG laser.<sup>5</sup>

We assessed the efficacy in glaucoma patients of laser trabeculoplasty using a new diode laser, and determined whether there is any difference in the results from this laser and those of the standard argon laser.

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### Material and Methods

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Twenty phakic eyes of 20 patients with primary open-angle glaucoma that was not controlled despite maximum tolerated medical therapy were randomly assigned to one of the two treatment groups. Informed consent was obtained from all patients.

In Group 1, ten eyes were treated with the diode laser. In Group 2 (ten eyes) laser trabeculoplasty was performed with the argon laser.

All eyes had wide open angles with a visible ciliary body band or scleral spur. None of the eyes had previously undergone surgical or laser treatments.

Each patient underwent a complete ophthalmic examination in the two weeks before laser trabeculoplasty. The examination included biomicroscopy of the anterior segment, gonioscopy, fundus examination by indirect ophthalmoscopy, and tonometry with the Goldmann applanation tonometer. Visual field testing was done with automated perimetry. Intraocular pressure was measured immediately before and two hours after laser trabeculoplasty.

Laser trabeculoplasty was performed by one of us (R.B.).

Topical anesthesia was administered (benoxinate hydrochloride 0.4%) before a Ritch trabeculoplasty four-mirror lens was placed over the eye.<sup>6</sup> Treatment consisted of a 0.1-second application of a 100- $\mu$ m (diode laser) or 50- $\mu$ m (argon laser) spot to the junction of the pigmented and nonpigmented trabecular meshwork for 360 degrees in one session. Power was set to create a blanching effect or a small vanishing bubble on the treatment site. Each treat-

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ment consisted of 20 to 25 applications per quadrant.

The study design specified that no changes in glaucoma medications were to be made after laser trabeculoplasty, to permit accurate assessment of the influence of the treatment on intraocular pressure without any possible influence from changes in medications. All patients were instructed to add topical corticosteroids three times a day for five days after the laser procedure. Six and 12 months after laser trabeculoplasty all patients underwent complete ophthalmic examination (including gonioscopy) by one of us (R.C.) who did not know which laser had been used for the laser trabeculoplasty. When the decision for laser trabeculoplasty was made, the intraocular pressure at the last visit was taken as the baseline intraocular pressure to be compared with the six- and 12-month follow-up measurements. Intraocular pressure measured immediately before the laser treatment was recorded as the preoperative intraocular pressure to be compared with the intraocular pressure two hours after laser trabeculoplasty.

Success was defined as the achievement of an intraocular pressure below 20% of the baseline value.

The actual and percentage changes in intraocular pressure for each eye were calculated, with the means and standard deviations. We used Student's paired *t*-test to compare the intraocular pressure follow-up after laser trabeculoplasty with baseline and preoperative values. The Mann-Whitney U test was used to compare the differences in intraocular pressure between the two groups. Correlations between different variables were investigated by using the Spearman correlation coefficient. For comparison between data we considered  $P < .05$  to be statistically significant. For all correlations we considered  $P < .10$  to be statistically significant.

### Results

The ten patients in Group 1 were all white (seven men and three women). The mean age was  $69.7 \pm 8.63$  years. All patients were treated with beta-blockers, two with epinephrine, three with pilocarpine 3% four times a day, seven with pilocarpine 4% four times a day, and four with 500 mg a day of carbonic anhydrase inhibitors. The ten patients in Group 2 were all

white (six men and four women). The mean age was  $71.9 \pm 8.58$  years. All patients were treated with beta-blockers, four with epinephrine, two with pilocarpine 3% four times a day, eight with pilocarpine 4% four times a day, and four with carbonic anhydrase inhibitors, 500 mg a day. No statistically significant differences were found between the groups for gender, race, and age. Basic data are shown in Table 1. The baseline, six- and 12-month intraocular pressure for both groups are shown in Figure 1. The mean intraocular pressure for both groups at different times of the study are shown in Table 2. Correlation between baseline intraocular pressure and the intraocular pressure difference at 12 months for both groups is shown in Figure 2.

In Group 1, laser trabeculoplasty was performed by using a mean energy of  $1135 \pm 66.9$  mW and a mean number of spots of  $86.6 \pm 5.87$ . No significant difference was found between the preoperative and two-hour values, but the decrease in intraocular pressure from the baseline value was highly significant at six months

**TABLE 1**  
INTRAOCULAR PRESSURES AFTER DIODE AND ARGON LASER TRABECULOPLASTY

INTRAOCULAR PRESSURE, MM HG								
PATIENT			PRE-	2	6	12	ENERGY,	
NO.	EYE	BASELINE	OPERATIVE	HRS	MO	MO	MW	SPOTS
Diode Laser Trabeculoplasty								
1	L	30	21	10	21	21	1,200	80
2	R	22	22	24	16	17	1,200	85
3	R	18	16	21	15	15	1,100	100
4	L	21	19	16	17	17	1,100	94
5	L	27	25	22	17	17	1,200	83
6	L	18	18	19	15	16	1,200	85
7	R	20	18	22	10	12	1,150	85
8	R	23	22	20	14	14	1,100	85
9	R	26	24	22	18	20	1,100	84
10	L	25	25	26	20	20	1,100	85
Argon Laser Trabeculoplasty								
11	R	25	26	21	19	19	650	84
12	L	22	18	21	19	16	650	80
13	L	28	25	19	17	20	650	83
14	L	19	19	19	17	17	600	92
15	R	23	22	21	15	15	650	83
16	R	25	22	27	19	20	650	80
17	L	24	32	32	16	18	750	92
18	L	16	16	18	10	11	750	80
19	L	26	22	24	16	14	750	80
20	L	26	25	25	28	—	650	90



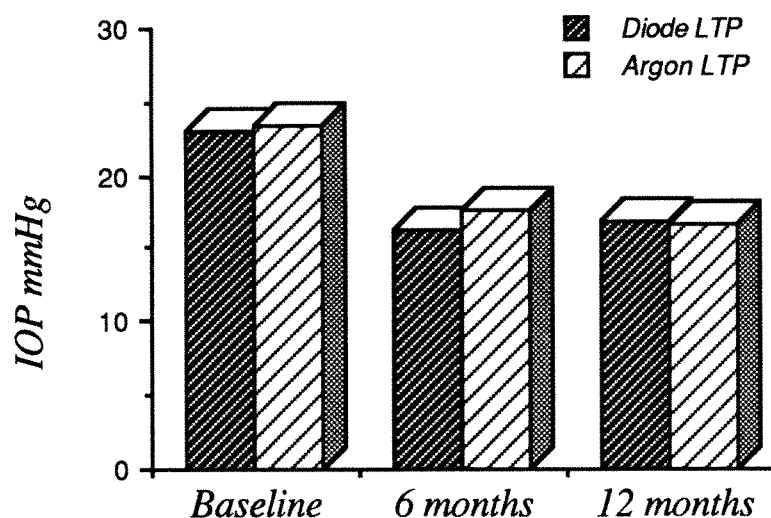


Fig. 1 (Brancato, Carassa, and Trabucchi). Mean intraocular pressures (mm Hg) at baseline, six months, and 12 months after diode laser trabeculoplasty and argon laser trabeculoplasty.

( $t = 7.49$ ;  $P = .0001$ ) and at one year ( $t = 6.97$ ;  $P = .0001$ ). Significant correlations were found between the intraocular pressure difference at one year and the baseline intraocular pressure ( $\rho = -.7706$ ;  $P = .0091$ ) and between the percent intraocular pressure difference at 12 months and age ( $\rho = +.5636$ ;  $P = .0877$ ). In this group the treatment was successful in seven of the ten patients.

In Group 2 laser trabeculoplasty was performed by using a mean energy of  $675.0 \pm 54.0$  mW and a mean number of spots of  $71.9 \pm 8.58$ . Six months after laser trabeculoplasty, one patient's pressure was uncontrolled and the patient underwent surgery. Thus, there were only nine of ten patients at the one-year follow-up. No significant difference was found between the pretreatment and the two-hour values, but the decrease in intraocular pressure from the baseline value was significant both at six months ( $t = 4.69$ ;  $P = .0001$ ) and at 12 months ( $t = 7.05$ ;  $P = .0001$ ).

Significant correlation was found between the intraocular pressure difference at 12 months and baseline intraocular pressure ( $\rho = -.6482$ ;  $P = .0575$ ). In this group the treatment was successful in eight of ten patients. Comparing Group 1 with Group 2, no significant differences were found between the baseline intraocular pressure and the preoperative, two-hour, six-, and 12-month values (only nine patients in Group 2). There were no notable differences between the intraocular pressure differences and the intraocular pressure percent differences at two hours, six months, and one year.

Between the diode and argon laser factors, a

significant difference was found for the energy ( $U = 155.0$ ;  $P = .0002$ ) but not for the number of spots used.

Mild iritis was present in almost all treated eyes, whereas intraocular pressure spikes were seldom seen in either group and were never greater than 5 mm Hg. At all follow-up examinations, peripheral anterior synechiae were not detectable on gonioscopy in either group.

TABLE 2  
MEAN INTRAOCULAR PRESSURES\* FOR DIODE AND ARGON LASER TRABECULOPLASTY TREATED EYES

INTRAOCULAR PRESSURE	DIODE LASER	ARGON LASER	MANN-WHITNEY†	
			U	P
Baseline	23.0±3.97	23.4±3.60	100	NS
preoperative	21.0±3.16	22.7±4.60	93	NS
2 hrs	20.2±4.49	22.7±4.35	97	NS
6 mo	16.3±3.13	17.6±4.53	96.5	NS
12 mo	16.9±2.85	16.7±3.00	89	NS
2 hrs – pretreatment	–0.8±4.57	0.0±3.00	100.5	NS
(Percent change)‡	(–2.5±7.30%)	(+1.3±14.8)		
6 mo – baseline	(–6.7±2.83%)	(–5.8±3.91%)	99.5	NS
(Percent change)‡	(–28.7±11.00%)	(–28.7±15.3%)		
12 mo – baseline	–6.10±2.77	–6.44±2.74	103.0	NS
(Percent change)‡	(–25.9±10.1%)	(–27.5±9.87%)		

\*Mean ± SD, mm Hg.

†NS indicates not significant.

‡Calculated as (2 hrs – preoperative) × 100/preoperative.

§Calculated as (6 mo – baseline) × 100/baseline.

¶Calculated as (12 mo – baseline) × 100/baseline.



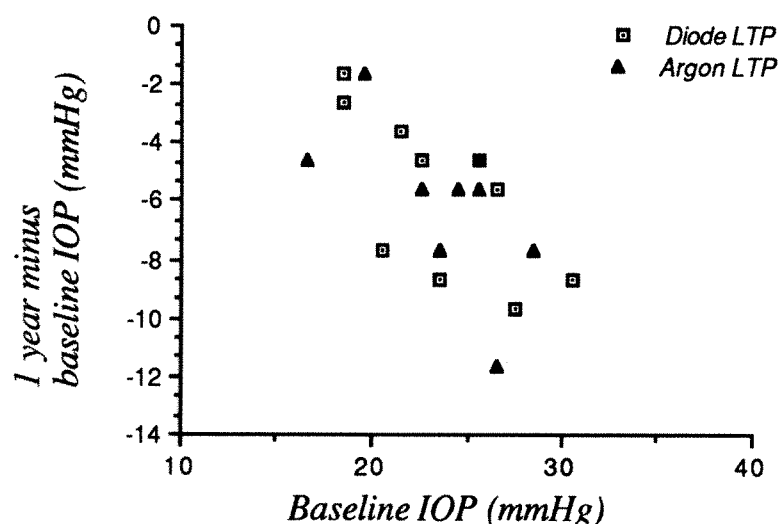


Fig. 2 (Brancato, Carassa, and Trabucchi). Correlation between baseline intraocular pressure and intraocular pressure difference at 12 months for both groups.

The only major complication was an angle hemorrhage in one eye treated with the diode laser.

### Discussion

Laser trabeculoplasty is an effective technique for lowering intraocular pressure in ocular hypertensives and in glaucoma. The procedure is usually performed by using a blue-green argon laser (488 to 514 nm) although monochromatic green argon laser (514 nm), krypton laser (647 nm), or Nd:YAG laser (1,064 nm) in thermal mode (free-running) have all proved to be effective.

Recently a diode infrared-emitting laser (810 nm) was introduced in ophthalmology.<sup>7</sup> Compared to the conventional laser systems currently used its advantages include compact size, standard voltage requirement, long operating life with low-cost maintenance, a simple air cooling system, and low cost.

We assessed the efficacy of laser trabeculoplasty on glaucoma patients with phakic eyes by using this new laser source and compared it with the efficacy of treatment with the blue-green argon laser.

The mechanism by which laser trabeculoplasty lowers intraocular pressure has not been clearly determined. The primary mechanism, proposed by Wise and Witter,<sup>1</sup> Brancato and associates,<sup>8</sup> and Rodrigues, Spaeth, and Donohoo,<sup>9</sup> is heat-induced collagen modification of the trabecular meshwork, which causes shrinkage of the lamellae and widening of the

intertrabecular spaces. Alternatively, since laser trabeculoplasty can remove trabecular cells, it may also stimulate cell division and renewal of the extracellular matrix with a resulting rejuvenation of the trabecular structure and consequent enhancement of aqueous outflow.<sup>10-12</sup> Both theories depend on the absorption of laser energy by the melanin pigments contained in the trabecular meshwork with resulting thermal coagulation.<sup>13</sup> Although the absorption curve for melanin is maximum for wavelengths between 400 and 700 nm, the infrared diode laser emitting at 810 nm has a demonstrated photocoagulative effect on the chorioretina by using higher energies.<sup>14-16</sup> Histologic studies on the effect of photocoagulation on the trabecular meshwork show that the appearance of diode and argon laser burns is similar, although the lesions from the diode laser are deeper.<sup>17</sup> We found that the diode laser lowered intraocular pressure when it was used to perform laser trabeculoplasty in phakic eyes with primary open-angle glaucoma both at six and at 12 months and that this effect was similar to that of a bichromatic argon laser. Defining success as the achievement of an intraocular pressure below 20% of the baseline value, the treatment was successful at one year in seven of the ten patients in Group 1, and in eight of the ten patients in Group 2. The mean percent intraocular pressure reduction from baseline was 25.9% in Group 1 and 27.5% in Group 2. These findings are consistent with those in laser trabeculoplasty with conventional ionized gas lasers, reported in other studies.<sup>18-20</sup> McHugh and associates<sup>21</sup> performed diode laser trabeculoplasty on 20 eyes of 13



patients, by using 180-degree burns with the Ritch lens or with the Goldmann three-mirror lens. Four eyes were subsequently treated in the remaining 180 degrees. The mean follow-up was eight months, and no randomized comparison with argon laser trabeculoplasty was carried out. Six months after the treatment the mean ocular hypotensive effect was 9.55 mm Hg, which corresponded to a 32% mean intraocular pressure reduction from baseline. These results are consistent with our finding of 28.7% lowering at six months. J. S. Schuman and associates (unpublished data) treated seven patients with diode laser trabeculoplasty and five with argon laser trabeculoplasty. The mean follow-up was one month and the intraocular pressure reduction was 5.8 and 6.0 mm Hg in the diode-treated and argon-treated groups, respectively. No significant differences between the two groups were found.

Previous studies reported positive correlations between the intraocular pressure decrease and the baseline value and between this decrease and age.<sup>22-26</sup> A significant correlation was found in each group between the intraocular pressure decrease at 12 months and the baseline intraocular pressure. Significant correlation between the percent intraocular pressure difference at 12 months and age was found in Group 1 but not in Group 2. A possible explanation may be the small sample size and the limited spread of the values.

The main differences between the diode and argon treatment concern the power setting and the spot size. Although both treatments were done with the Ritch lens, the mean power settings for diode laser trabeculoplasty and for argon laser trabeculoplasty were 1,135 mW and 675 mW, respectively. This difference could be related to the different photocoagulative effect of the two wavelengths on the treatment site: the diode laser causes deeper lesions than the argon laser. Thus, in order to reach the same visible blanching effect, the diode laser requires more power than the argon laser. Since the maximum power output in the diode laser is 1,200 mW, in no patient was bubble formation visible.

The second difference between the two treatments is the spot size. Laser trabeculoplasty protocols suggest a 50- $\mu$ m size but the diode laser's minimum available spot size is 100  $\mu$ m. This difference does not appear to influence the outcome of treatment, perhaps because a given spot size with any laser produces a wide range of lesion diameters, depending on the laser

used and on the focus.<sup>27</sup> Moreover, by using the Ritch lens the spot size was theoretically reduced 30% in both groups.<sup>6</sup>

The most serious complication of laser trabeculoplasty<sup>28</sup> is postoperative intraocular pressure increase, which, although common is mild and of short duration.<sup>29,30</sup> In our study the maximum intraocular pressure increase two hours after treatment was 5 mm Hg in both groups and the difference between the preoperative and the two-hour intraocular pressure was never significant. This finding is consistent with that of other studies in which intraocular pressure spikes were seldom reported when laser trabeculoplasty was performed anteriorly.<sup>31,32</sup> A frequent complication found in both groups was mild iritis, which is easily controlled with topical corticosteroids.

Peripheral anterior synechiae have been reported as a complication of laser trabeculoplasty, which occurs in 10% to 50% of all cases. In our study no peripheral anterior synechiae were found in either group during follow-up. This may be because of the anterior treatment<sup>33,34</sup> and the selection of patients, all of whom had wide open angles.

The only difference between the complications in the two groups was an angle hemorrhage reported in one eye during treatment with the diode laser. This hemorrhage was probably caused by an accidental lesion to an angle vessel not clearly seen during the procedure. The low visibility through the laser hole of the delivery system<sup>16</sup> was one of the main problems reported by the operator. The angle structures were often not clearly visible and it was difficult to detect the photocoagulative effect on the trabecular meshwork. Moreover, the delivery system (attached to the tonometer stand of the slit lamp) sometimes came into contact with the chin rest, which makes it difficult to focus the eye. Adaptations to the design of the instrument will surely overcome these problems.

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# Evaluation of Once-Daily Levobunolol 0.25% and Timolol 0.25% Therapy for Increased Intraocular Pressure

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In a three-month, double-masked, randomized clinical trial, we evaluated the once-daily ocular hypotensive efficacy of 0.25% levobunolol and 0.25% timolol in 80 patients with open-angle glaucoma or ocular hypertension. Thirty-seven of the 39 patients (95%) in the 0.25% levobunolol group and 35 of the 41 patients (85%) in the 0.25% timolol group successfully completed the three-month study period. The overall mean decrease in intraocular pressure was 5.3 mm Hg (22%) in the 0.25% levobunolol group and 5.4 mm Hg (22%) in the 0.25% timolol group. This difference was not statistically significant. In both treatment groups, effects on mean heart rate and blood pressure were minimal. The data suggest that levobunolol 0.25% and timolol 0.25%, administered once daily, are equally effective in the treatment of open-angle glaucoma and ocular hypertension.

**T**WO MAJOR AREAS OF CONCERN in glaucoma treatment with beta-blockers are systemic safety and compliance. A twice-daily regimen of

0.5% timolol or levobunolol is the recommended maximum dosage schedule for topical beta-blocker use in the treatment of glaucoma. Reducing the concentration or frequency of the dosage of topical beta-blockers is desirable, given the possibility of reducing systemic side effects. Additionally, a once-daily regimen might lead to better patient compliance and thus to a more effective overall treatment. Previous studies support the efficacy of once-daily administration of 0.5% levobunolol and 0.5% timolol for the control of increased intraocular pressure.<sup>1-3</sup> Lower concentrations of both drugs (0.25%) have also been effective when administered on a twice-daily basis.<sup>4</sup> In an open-label noncomparative study, the intraocular pressure of 21 of 29 (72%) of patients enrolled was adequately controlled with 0.25% levobunolol once daily, with an average intraocular pressure reduction of 24% from an unmedicated baseline value of 26.2 mm Hg.<sup>5</sup> For these reasons, we evaluated 0.25% levobunolol and 0.25% timolol in a well-controlled study to determine if these lower concentrations would be effective in controlling intraocular pressure when administered on a once-daily basis.

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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## Patients and Methods

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We conducted a multicenter, randomized, double-masked, parallel clinical trial of three months' duration. Patients with chronic open-angle glaucoma or ocular hypertension with unmedicated intraocular pressure measurements ranging from 22 to 32 mm Hg were selected from the clinic population available to the investigators. Those excluded from study participation included the following: patients whose increased intraocular pressure was not

controlled by single-drug therapy; women who were of childbearing potential, were pregnant, or were nursing mothers; and patients with cardiovascular or pulmonary contraindications to beta-blocker usage. Patients receiving ocular hypotensive therapy before the initiation of the study underwent a washout period of two weeks if they had been taking beta-adrenergic antagonists or adrenergic agonists or four days if they had been taking miotics or carbonic anhydrase inhibitors. Before study entry, patients provided written informed consent.

At the prestudy examination, intraocular pressure, visual acuity, heart rate, and blood pressure were measured, and biomicroscopic, ophthalmoscopic, and visual field (automated static) examinations were performed. At the baseline (postwashout) examination, intraocular pressure, visual acuity, heart rate, and blood pressure were measured, and a biomicroscopic examination was performed. After the baseline examination, patients received a bottle of masked medication, either 0.25% levobunolol or 0.25% timolol, and were instructed to instill their medication once daily between the hours of 7:00 A.M. and 9:00 A.M. for a three-month period.

Patients returned for follow-up examinations at two weeks, and at one, two, and three months. Follow-up visits were scheduled in the morning and performed before drug instillation. Thus, each patient was examined approximately 24 hours after receiving medication.

In the statistical analysis of the data, we averaged the intraocular pressure values of both eyes when the intraocular pressure of each was at least 22 mm Hg; otherwise, we analyzed only the eye with a baseline value of at least 22 mm Hg. We used a two-way analysis of variance, including drug and investigator main effects and drug-by-investigator interaction, to compare treatments for intraocular pressure at baseline and mean changes from baseline in intraocular pressure, heart rate, and systolic and diastolic blood pressure. We used a repeated measures analysis of variance model to compare overall mean changes in intraocular pressure. Overall mean changes were based on least squares means of the repeated measures analysis of variance. The overall means were adjusted for investigator, drug, week, and the interaction effects of the main effects.<sup>6</sup> For all statistical analyses, a P value of .05 or less was considered statistically significant.

## Results

Eighty patients with ocular hypertension or chronic open-angle glaucoma were included in the study analysis: 39 patients were treated once daily with levobunolol 0.25% and 41 patients were treated once daily with timolol 0.25% (Table 1). Ten additional patients were excluded from the statistical analysis for reasons unrelated to the study medication.

Mean age was significantly greater in the timolol treatment group than in the levobunolol treatment group ( $P = .01$ ). There was a significantly higher proportion of black patients in the levobunolol treatment group than in the timolol treatment group ( $P = .045$ ). Analysis of covariance was performed because of these observed differences. No relationship was found between mean age and mean intraocular pressure reduction or between race and mean intraocular pressure reduction. No significant differences were seen between the treatment groups with respect to the number of

TABLE 1  
PATIENT DEMOGRAPHICS

	0.25% LEVOBUNOLOL (N = 39)	0.25% TIMOLOL (N = 41)
Age (yrs)		
Mean $\pm$ S.D.	59.4 $\pm$ 13.4	65.6 $\pm$ 9.72
Range	25-81	39-85
Race		
White	27	36
Black	11	5
Asian	1	0
Gender		
Male	18	18
Female	21	23
Iris color*		
Light	19	22
Dark	19	19
Not recorded	1	0
Diagnosis		
Bilateral open-angle glaucoma	21	26
Bilateral ocular hypertension	12	10
Open-angle glaucoma in one eye and ocular hypertension in the other	5	5

\*Light irides = blue, green, or hazel; dark irides = brown.



patients receiving glaucoma medication before study entry.

Thirty-seven of the 39 patients (95%) in the 0.25% levobunolol group and 35 of the 41 patients (85%) in the 0.25% timolol group successfully completed the three-month study. One of the 39 patients (3%) in the 0.25% levobunolol group and three of the 41 patients (7%) in the 0.25% timolol group were eliminated from the study because of inadequately controlled intraocular pressure. Two patients, both in the 0.25% timolol group, were eliminated from the study because of adverse reactions, including headaches, general listlessness, and shortness of breath upon exertion in one patient and only shortness of breath upon exertion in the other patient. Two additional patients, one in each of the treatment groups, were discontinued because of their inability to meet the study schedule. All eight subjects who did not complete the study were included in the analysis up to the point of their departure from the study.

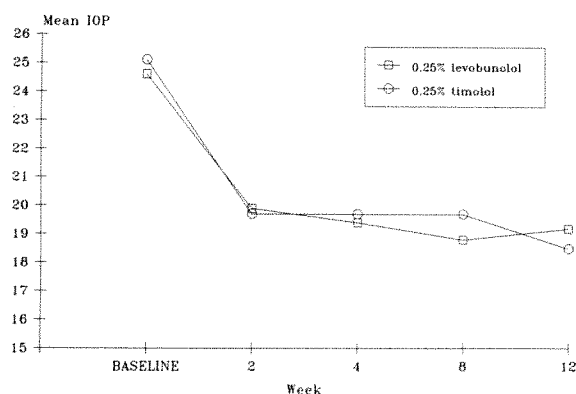
Mean intraocular pressure values at baseline (24.7 mm Hg in the 0.25% levobunolol group and 25.1 mm Hg in the 0.25% timolol group) were not significantly different between the treatment groups (Fig. 1, Table 2). At follow-up visits, statistically significant mean decreases ranged from 4.7 to 5.8 mm Hg in the 0.25% levobunolol group and from 5.4 to 6.6 mm Hg in the 0.25% timolol group. Overall mean intraocular pressure decreases (least-squares means from repeated measures analysis) for the three-

**TABLE 2**  
MEAN CHANGES FROM BASELINE OF INTRAOCULAR PRESSURE (MM HG\*)

STUDY PERIOD (RANGE)	0.25% LEVOBUNOLOL		0.25% TIMOLOL	
	NO.†	MEAN ± S.D. (RANGE)	NO.†	MEAN ± S.D. (RANGE)
Day 0 (baseline)	39	24.7 ± 2.3 (22-30)	41	25.1 ± 2.9 (22-32)
Week 2	33	-4.7 ± 2.8 (-12-2.5)	32	-5.4 ± 3.3 (-17.5-3)
Week 4	32	-5.2 ± 3.0 (-11.5-0.5)	30	-5.4 ± 3.4 (-13.5-0.5)
Week 8	30	-5.8 ± 2.5 (-11-0)	31	-5.4 ± 3.6 (-17-1)
Week 12	35	-5.4 ± 2.0 (-10-2)	35	-6.6 ± 3.0 (-18.5-1.5)
Overall mean change		-5.3		-5.4

\*Intraocular pressure decreased significantly from baseline in both treatment groups at each follow-up visit. There was no statistically significant difference between the groups at any visit ( $P > .05$ ) or overall mean ( $P = .880$ ). There was no significant treatment site interaction throughout the study period.

†Changes in number of patients at each visit were because of subject withdrawal from the study and missed or late follow-up visits.

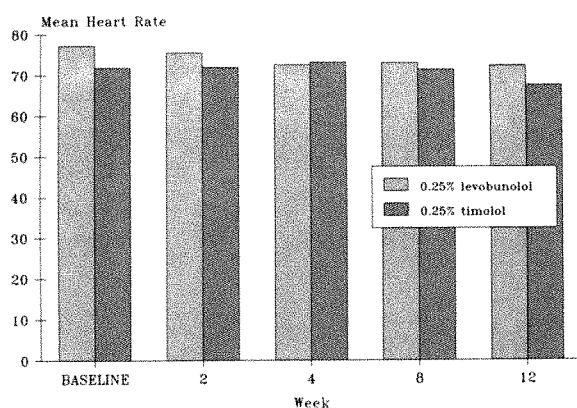


**Fig. 1** (Silverstone and associates). Mean intraocular pressure (IOP) of patients with open-angle glaucoma or ocular hypertension during three-month treatment with once-daily levobunolol or once-daily timolol.

month period were 5.3 mm Hg in the 0.25% levobunolol group and 5.4 mm Hg in the 0.25% timolol group. There were no significant differences between the treatment groups at any of the follow-up visits or for the overall mean decrease. The statistical power to detect a 2-mm Hg, between-group difference in overall mean values was approximately 87%.

Mean heart rate decreased slightly in both treatment groups (Fig. 2). Significant decreases from baseline in mean heart rate were observed in the 0.25% levobunolol group at Weeks 4 and 12 and in the 0.25% timolol group at Week 12. There were no significant differences with regard to mean heart rate between the treatment groups at any follow-up visit ( $P > .05$ ) or for the overall mean change ( $P = .343$ ).

Mean systolic blood pressure decreased slightly in both treatment groups; however, these decreases were not statistically significant. Overall mean diastolic blood pressure decreased slightly in the 0.25% timolol group and increased slightly in the 0.25% levobunolol



**Fig. 2** (Silverstone and associates). Mean heart rate of patients with open-angle glaucoma or ocular hypertension during three-month treatment with once-daily levobunolol or once-daily timolol.

group. These differences in mean changes were not significant. A significant within-group decrease was observed in the 0.25% timolol group at Week 2. There were no significant within-group changes from baseline observed in the 0.25% levobunolol group.

## Discussion

Twice-daily instillation of topical beta-blockers is frequently used in the treatment of open-angle glaucoma or ocular hypertension. Recently, however, it has been demonstrated that topically applied beta-blocking agents may exert their influence on intraocular pressure for a longer period of time than was once thought.<sup>7,8</sup> Additionally, several studies have shown that both timolol and levobunolol are effective in a large percentage of the population tested when administered on a once-daily basis.<sup>1-3,9,10</sup>

In our study, which directly compared once-daily administration of 0.25% timolol and 0.25% levobunolol, we found that there was virtually no difference between the treatment groups with regard to mean intraocular pressure decreases or the percentage of patients with controlled intraocular pressure. Overall percentage reductions in intraocular pressure (22% for each of the two treatment groups) were similar to those seen in a previous study that evaluated once-daily administration of 0.5% levobunolol (23% reduction) and 0.5% timolol (26% reduction), which suggests a simi-

lar efficacy profile between the 0.5% and 0.25% concentrations of these two topical beta-blockers.<sup>3</sup> In another study, levobunolol 0.5% instilled once daily was compared with levobunolol 0.5% instilled twice daily.<sup>11</sup> This study disclosed no significant difference in mean intraocular pressure reduction between treatment groups at any follow-up visit or with respect to the overall mean, which suggests that there is similar efficacy between once-daily and twice-daily regimens of levobunolol. These data indicate that once-daily treatment with topical levobunolol 0.25% or timolol 0.25% is effective in controlling intraocular pressure in open-angle glaucoma or ocular hypertension and may be comparable to once-daily or even twice-daily treatment with the 0.5% concentrations of levobunolol or timolol.

Systemic safety between the two treatment groups was similar. There were no significant differences between the groups with respect to mean heart rate or systolic or diastolic blood pressure at any follow-up visit or with regard to the overall mean. Mean changes in blood pressure from baseline did not reach the level of significance in either treatment group, whereas mean heart rate decreased significantly in the 0.25% levobunolol group at Weeks 4 and 12 and in the 0.25% timolol group at Week 12.

We conclude that once-daily administration of 0.25% levobunolol and 0.25% timolol are equivalent with respect to ocular hypotensive efficacy and systemic and ocular safety in this population of patients with mild to moderately increased intraocular pressure. Our results suggest that once-daily administration of either 0.25% levobunolol or 0.25% timolol is an effective therapy in controlling increased intraocular pressure. The percentage reduction in intraocular pressure was similar to that seen in previous studies of once-daily administration with the 0.5% concentration of levobunolol or timolol as well as twice-daily treatment with the 0.25% concentration of these agents.

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#### OPHTHALMIC MINIATURE

The qualities of hand which are combined in an accomplished eye-operator may be summed up under the following heads, each of which will demand a brief separate consideration:—

1. A high development of what is called by physiologists "muscular sense"—the faculty by which we feel and estimate the degree of force we are exerting, either in pressure or traction.

2. The power of uniting the two hands in consentaneous movement, and of directing the intelligence to them simultaneously; so that they may work smoothly and harmoniously together as a single organ for the attainment of a common object, and may both at once be equally under the control and governance of the will.

3. The power to employ the left hand, indifferently with the right, for the guidance and use of cutting or other instruments.

4. Steadiness

Robert Brudenell Carter, *A Practical Treatise on Disease of the Eye*  
London, Macmillan, 1875, p. 150

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# Human Papillomavirus Type 16 DNA in Ocular and Cervical Swabs of Women With Genital Tract Condylomata

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Gerald Bernstein, M.D., and Yan Yu Sun, M.D.

Human papillomavirus type 16 is associated with dysplasias and carcinomas of the conjunctiva and of the uterine cervix. To explore the relationship between cervical and ocular human papillomavirus infection, we examined DNA from bilateral limbal swabs and cervical swabs from 17 women (age range, 17 to 46 years; median, 31.7 years) with biopsy-proven human papillomavirus-related cervical dysplasia who had a normal ocular surface. Using polymerase chain reaction, we identified human papillomavirus 16 DNA in one or both eyes of 13 (76.5%) patients, six (46.2%) of whom had demonstrable human papillomavirus 16 DNA in cervical swabs as well. It thus appears that human papillomavirus 16 is present in the conjunctivae of some patients with human papillomavirus-related genital warts who have no ocular manifestations of infection. Although autoinoculation of conjunctiva may be the source of some ocular human papillomavirus, data suggest that other modes of transmission to the eye also exist. Additional study of the epidemiologic characteristics of ocular human papillomavirus, a widely prevalent virus known to be associated with dysplasias/atypias and cancer, is warranted.

**H**UMAN PAPILLOMAVIRUSES are responsible for an epidemic of sexually transmitted disease in the United States, with an estimated 12 million

people currently being treated for anogenital lesions and millions more with inapparent or quiescent infection.<sup>1</sup> Approximately 750,000 human papillomavirus-related genital tract lesions are diagnosed each year. Over 50 distinct strains of human papillomavirus have been identified,<sup>1</sup> some of which, particularly types 16 and 18, have been implicated in the development of several carcinomas in humans, including those in the uterine cervix, anogenital region, upper respiratory tract, and skin.<sup>2</sup>

Human papillomavirus DNA from types 6 and 11, commonly associated with respiratory papillomatosis and benign anogenital condylomata, are also present in conjunctival papillomas,<sup>3-6</sup> which indicates an association between human papillomavirus and ocular lesions. Human papillomavirus type 16 DNA has recently been identified in squamous dysplasias and carcinomas of the conjunctiva and cornea<sup>7</sup> and of the eyelid,<sup>8</sup> and other conjunctival dysplasias have been shown to contain DNA from both human papillomavirus 16 and 18.<sup>9</sup> Although transmission of human papillomavirus to the cervix and anogenital region is through intimate contact,<sup>1</sup> it is not clear how the infection reaches the conjunctiva. Some sexually transmitted diseases, such as chlamydia, can be transmitted to the eye through hand-eye contact.<sup>10</sup> We attempted to determine whether or not such a mode of transmission might be possible for human papillomavirus and specifically whether individuals with human papillomavirus-related cervical infection and lesions might also have asymptomatic ocular human papillomavirus infection.

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## Patients and Methods

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We studied 17 patients who were examined at the Outpatient Gynecology Clinic at Los Angeles County/University of Southern California Medical Center for clinically evident cervical

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lesions, presumed to be of human papillomavirus origin, or biopsy-proven condylomata. Patients were examined for the study when they came to the clinic for examination after treatment of the cervical lesions.

After obtaining informed consent, a slit-lamp examination of the anterior segment was performed on each patient. Limbal swabs were then performed after a drop of topical anesthetic was applied. A sterile cotton swab was gently passed over the inferior corneoscleral limbus and inferior fornix of each eye and immediately placed in sterile, cell-free virus transport medium. Samples from each eye were obtained with separate cotton swabs and placed in separate vials.

Cervical swabs of cervical lesions were performed. After placement of an unlubricated speculum, a sterile cotton swab was passed gently across the endocervix and exocervix and then immediately placed in sterile, cell-free virus transport medium. Vials were stored at 4 C until DNA analysis.

Polymerase chain reaction was performed as described previously.<sup>7</sup> Briefly, the contents of each vial were boiled to extract DNA. An aliquot was added to individual microcentrifuge tubes already containing 100  $\mu\text{mol/l}$  of each deoxyribonucleotide, 10 mmol of Tris buffer (pH 8.3), 50  $\mu\text{mol/l}$  of potassium chloride, 1.5

$\mu\text{mol/l}$  of magnesium chloride, and 5  $\mu\text{g}$  per tube of gelatin as stabilizer. Each reaction mixture contained a pair of oligonucleotide primers specific for human papillomavirus type 16 or 18,<sup>11</sup> at a concentration of 1  $\mu\text{mol/l}$ , and two units of AmpliTaq DNA polymerase (Perkin Elmer Cetus, Emeryville, California). The reaction mixture was overlaid with an equal volume of mineral oil. Temperature cycling consisted of denaturation at 94 C, annealing of oligonucleotides at 50 C for two minutes, and primer extension at 72 C for one minute. Twenty-five cycles were carried out for human papillomavirus 16; 30 cycles were done for human papillomavirus 18. Aliquots of the aqueous phase were analyzed by dot blot hybridization.

For hybridization of amplified DNA, 5  $\mu\text{l}$  of aqueous phase product was mixed with 250  $\mu\text{l}$  of a denaturation solution consisting of 0.4 N sodium hydroxide and 25 mmol of ethylenediaminetetraacetic acid. The mixture was applied to nylon-filter membranes (Oncor, Gaithersburg, Maryland) with a dot blot apparatus (Oncor). Samples were washed, and the DNA was fixed by baking at 80 C under 16 cm of water vacuum for two hours. Hybridization with <sup>32</sup>P-labeled probes specific for human papillomavirus type 16 or 18 was performed as described previously.<sup>11</sup>

Positive controls included commercially available whole-genome DNA from human papillomavirus types 16 and 18 (Oncor) and conjunctival tissue samples known to be positive for human papillomavirus DNA.<sup>7</sup> Negative controls included paraffin sections from a conjunctival melanoma and three samples of ligneous conjunctivitis, processed as described previously.<sup>7</sup> Additional negative controls included two vials run through the polymerase chain reaction, dot blot, and hybridization that contained all elements except target DNA or Taq polymerase, respectively, and in which these elements were replaced with an equal volume of distilled water.

## Results

Swabs were obtained from the right eye, left eye, and cervix from 17 women who ranged in age from 17 to 46 years, with a median age of 31.7 years. Sixteen (94.1%) were Hispanic, and one (5.9%) was black. The duration of medically documented cervical lesions ranged from one month to ten years with a median duration

**TABLE 1**  
HUMAN PAPILLOMAVIRUS 16 DNA IN SWABS OF  
LIMBUS AND CERVIX

CASE NO., AGE (YRS), ETHNICITY*	R.E.	L.E.	CERVIX
1, 20, H	Absent	Present	Absent
2, 46, H	Absent	Absent	Absent
3, 36, H	Present	Present	Absent
4, 23, H	Present	Present	Present
5, 27, H	Present	Absent	Absent
6, 31, H	Absent	Absent	Absent
7, 28, H	Present	Absent	Present
8, 39, H	Absent	Present	Present
9, 23, B	Present	Absent	Absent
10, 17, H	Present	Present	Absent
11, 29, H	Present	Absent	Absent
12, 31, H	Present	Absent	Present
13, 39, H	Absent	Present	Absent
14, 43, H	Present	Absent	Absent
15, 40, H	Absent	Absent	Absent
16, 35, H	Present	Present	Present
17, 29, H	Absent	Absent	Absent

\*H equals Hispanic; B equals Black.

of 21.6 months. All patients had abnormal results of Papanicolaou smears suggestive of human papillomavirus infection or condyloma. None of these women had a history of ocular problems.

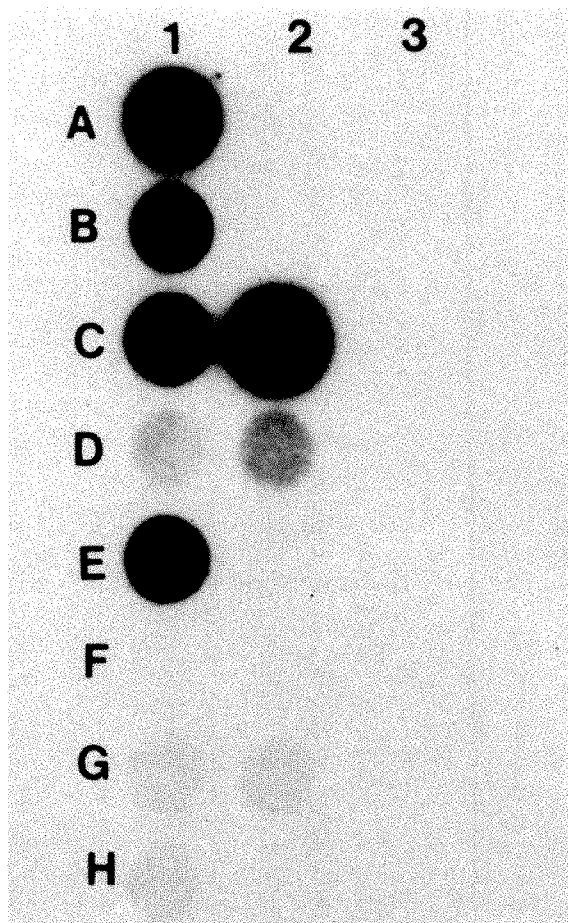
Ocular examination disclosed no abnormalities in any of the 17 women. Colposcopic examination with biopsies of cervix or endocervix confirmed the presence of condyloma in 16 (94.1%) patients. The single patient without condylomata had cervical intraepithelial neoplasia grade III (cervical intraepithelial neoplasia III)/carcinoma in situ (full-thickness epithelial atypia) on examination of tissue from the endocervical canal.

DNA from human papillomavirus 16 was identified in ocular specimens from 13 (76.5%) of the 17 patients (Table 1). In six (35.3%) patients, human papillomavirus 16 DNA was detected in only the right eye, and three (17.6%) patients had DNA present in only the left eye. Four (23.5%) patients had human papillomavirus 16 DNA present bilaterally (Figures 1 and 2).

Six (35.3%) patients had cervical swabs positive for human papillomavirus 16 DNA. Three of these had human papillomavirus DNA present also in both eyes, two had human papillomavirus DNA in only the right eye, and the sixth was strongly positive for human papillomavirus in the left eye only. Every patient in whom human papillomavirus was identified in the cervix had human papillomavirus-positive conjunctivae, but seven (53.8%) of the patients with human papillomavirus 16-positive conjunctivae did not have human papillomavirus 16 DNA in their cervical swabs.

Human papillomavirus 18 DNA was present in the right eye of one (9.1%) patient, who also had human papillomavirus 16 DNA bilaterally but whose cervix was negative for human papillomavirus 16. Human papillomavirus 18 was present in the cervix of another patient with human papillomavirus 16-positive conjunctivae and cervix (Table 2). All other samples tested were negative for human papillomavirus 18 DNA.

Controls of human papillomavirus 16 or 18 DNA were positive when reacted with type 16 and 18 primers and probes, respectively. Specimens of conjunctival melanoma and ligneous conjunctivitis were negative for human papillomavirus types 16 and 18 DNA, as were reactions run without target DNA and reactions containing type 16 or 18 whole-genome DNA but no Taq.

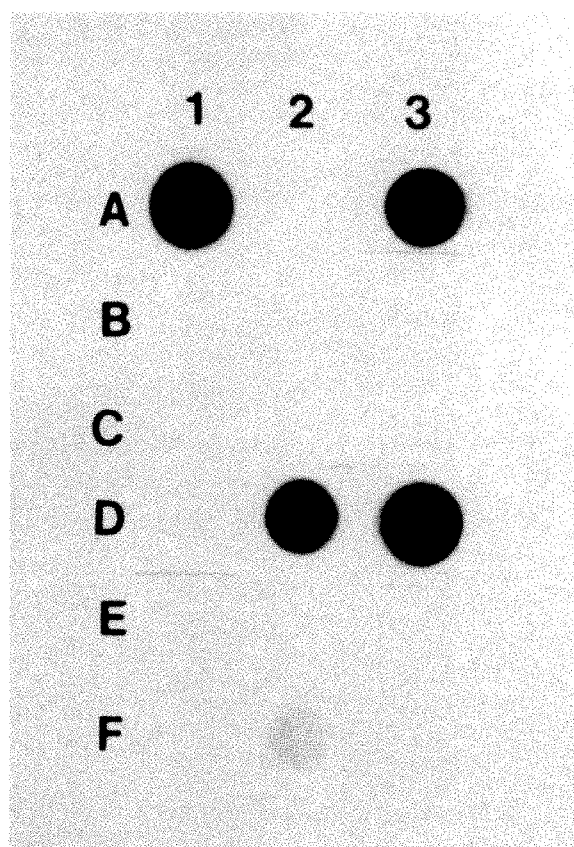


**Fig. 1** (McDonnell and associates). Dot blots of polymerase chain reaction product, using human papillomavirus 16 primers, hybridized to  $^{32}$ P-labeled human papillomavirus 16 probe. Data from two patients are illustrated as follows: Case 8 (F1 to H1), right eye is negative (F1), left eye and cervix are positive (G1 and H1, respectively). Case 11 (D2 to F2), right eye is positive (D2), left eye and cervix are negative. Additional samples represent controls: A1, human papillomavirus 16 DNA 0.5 ng; B1 to E1, positive tissue controls; A2, no DNA; C2, human papillomavirus 16 DNA 0.5 ng; G2, human papillomavirus 16 DNA 0.001 ng; H2, human papillomavirus 16 DNA, no Taq. Exposure time was 22 hours.

## Discussion

We identified human papillomavirus type 16 or 18 DNA in ocular swabs from 13 (76.5%) of 17 women with clinically evident, biopsy-proven, human papillomavirus-related genital tract condylomata or dysplasia. In six (46.2%) of these 13 women, the same human papillomavi-





**Fig. 2** (McDonnell and associates). Dot blots of polymerase chain reaction product; data from three additional patients. A composite was made from different parts of a larger membrane to illustrate the results of duplicate polymerase chain reactions on two of the patients. Case 5 (A1 to C1, A3 to C3) has positive right eye on two different polymerase chain reactions (A1, A3), and left eye and cervix are negative (B1, C1; B3, C3). Case 2 had no identifiable human papillomavirus 16 DNA in any of the three swabs on two separate polymerase chain reactions (D1 to F1, A2 to C2). Case 7 had positive swabs of the right eye and cervix (D2 and F2, respectively), but the left eye was negative (E2). D3, human papillomavirus 16 DNA; E3, no DNA.

rus type was present in cervical swabs. None of the patients had any evidence of ocular disease on slit-lamp examination of the anterior segment. These findings suggest several novel concepts regarding the possible role of human papillomavirus in ocular surface neoplasia and raise many more questions.

Human papillomavirus can exist without gross evidence of disease in the anogenital tract. Using polymerase chain reaction, filter in situ hybridization, or Southern blotting, Melchers and associates<sup>12</sup> found a 5% to 12% inci-

dence of DNA from several types of human papillomavirus in cervical samples from women with no overt cervical abnormalities; the types most frequently identified were 6, 11, 16, and 18, human papillomavirus types previously shown also to be associated with ocular lesions.<sup>3-9</sup> We reported DNA from human papillomavirus 16 in uninvolved and involved eyes of a patient with unilateral conjunctival epithelial dysplasia or carcinoma,<sup>7</sup> (and unpublished data) which establishes that human papillomavirus can similarly exist in the conjunctiva in the absence of an overt lesion. We have now demonstrated human papillomavirus 16 or 18 DNA in the apparently uninvolved conjunctivae of women with genital tract lesions presumed to be of human papillomavirus origin.

Human papillomavirus DNA appears to exist in only one eye in some of the women we studied. Additionally, slightly over one half of the patients with unilateral or bilateral conjunctival human papillomavirus 16 had no demonstrable human papillomavirus 16 DNA on cervical swabs, even though cervical lesions were present both clinically and on biopsy of the cervix (Table 1). A variety of human papillomavirus types are associated with cervical lesions,<sup>2</sup> and it is not unusual for a patient to have simultaneous infections with more than one human papillomavirus type in the genital tract alone.<sup>13</sup> Recurrent condyloma may be associated with a human papillomavirus type different than that of an earlier lesion, which indicates that the human papillomavirus complement detectable in a given patient may vary over time, perhaps representing new infections.<sup>14</sup> In a recent report, human papillomavirus 16 and 18 were both identified in two of five conjunctival epithelial tumors,<sup>9</sup> and in our study there were two patients who had both human papillomavirus 16 and 18 in the same conjunctival swab. It thus appears that several different human papillomavirus types may infect the same individual at one or more body sites, and although one type is present in the genital tract, another type may infect the conjunctiva. We did not test for human papillomavirus 6, 11, 31, or 33, or for other types associated with clinically evident anogenital lesions.<sup>2</sup> Cervical condylomata and dysplasia are almost uniformly associated with human papillomavirus, and our negative results for human papillomavirus 16 in some patients suggest that other human papillomavirus types are present in the cervix in these women.

Based upon the absence of human papilloma-

virus 16 and 18 DNA in the cervical swabs from seven (53.8%) of the 13 women with subclinical infection of the conjunctiva, it appears that in only six (46.2%) patients it is feasible that the women infected their own conjunctivae with cervical human papillomavirus 16 through hand-to-eye contact or a systemic infection. This may imply that ocular infection in the other women was not contracted through self-inoculation but by some other mode of transmission. In one patient whose Papanicolaou smear results had been abnormal for ten years before sampling of the cervix for polymerase chain reaction, it is possible that the human papillomavirus type now in the eye may have been transmitted from an initial cervical infection that was successfully treated and no longer amenable to sampling. In most of the patients, the time course between abnormal Papanicolaou smear results and biopsy precludes such an interpretation. Thus, although anogenital human papillomavirus is clearly a sexually transmitted infection, the way that human papillomavirus reaches the eye, and therefore the population at risk for such infection, is unknown.

The patients we previously described who had human papillomavirus-positive conjunctival neoplasms or swabs were older (median age, 65 years), and most were male.<sup>6,7</sup> All had conjunctival or corneal lesions that were severe enough to lead them to seek medical attention and to necessitate surgery. The current study demonstrates that human papillomavirus may also be present in individuals who have no overt conjunctival disease, at a younger median age than that reported for dysplasias (31.5 years in the current study). If, as we believe, human papillomavirus is somehow related to the development of conjunctival dysplasias and carcinomas,<sup>7</sup> such individuals may be at risk of developing conjunctival epithelial neoplasia. If this is the case, it would be a striking departure from current thinking about the patient group at risk of developing conjunctival epithelial neoplasia.

There are several possible explanations for the discrepancy. It may be that there is a long interval between human papillomavirus infection of the conjunctiva and development of epithelial lesions. This would explain why conjunctival epithelial neoplasia is an uncommon process seen only in the elderly, but it would not explain its overwhelming propensity to occur in men.<sup>15</sup>

Alternatively, our findings may herald an increased incidence of conjunctival squamous diseases in younger people, including a number of women. On the basis of such evidence,<sup>3-7,9</sup> we now know that certain human papillomavirus types thrive in the conjunctival epithelium. With other organisms capable of infecting both the genital tract and the eye, such as chlamydia and syphilis, epidemics of sexually transmitted disease involving the genital tract are rapidly followed by similar epidemics of ocular disease.<sup>10,15</sup> Studies indicate more and more women develop sexually transmitted human papillomavirus infections of the genital tract, and infections are developing at a younger age.<sup>16</sup> The median age for development of invasive cervical carcinoma is also declining.<sup>16</sup> The changing epidemiologic characteristics of human papillomavirus infection should be expanded to include the conjunctiva, and our patients may be the earliest manifestation of a future epidemic of ocular human papillomavirus infection and human papillomavirus-related lesions, particularly among young people whose lifestyles render them susceptible to contracting sexually transmitted infections.

The significance of human papillomavirus-positive conjunctival swabs for individual patients is unclear, although some human papillomavirus types may play a role in the development of conjunctival epithelial neoplasia. Human papillomavirus does not appear to be eradicated from the cervix of some patients over time.<sup>17</sup> If the same is true of conjunctival human papillomavirus infection, our patients potentially have many years ahead of them during which they may develop conjunctival

TABLE 2  
HUMAN PAPILLOMAVIRUS 16 AND 18 DNA IN SWABS OF THE CORNEOSCLERAL LIMBUS AND CERVIX

PATIENT	R.E.		L.E.		CERVIX	
	16	18	16	18	16	18
3	Present	Absent	Present	Present	Absent	Absent
4	Present	Absent	Present	Absent	Present	Present



human papillomavirus-related neoplasia. Whether or not such lesions develop may depend upon the relative roles played by human papillomavirus and other factors in the development of neoplasia. Only large epidemiologic studies conducted over many years will disclose the potential effects of human papillomavirus in the conjunctivae of these and other asymptomatic individuals and will identify factors that may be involved in contracting ocular human papillomavirus infection and in the development of conjunctival epithelial neoplasia.

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# Diurnal Intraocular Pressure After Successful Primary Laser Trabeculoplasty

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Tor Elsås, M.D., Hanna Junk, M.D., and Harald Johnsen, M.D.

In 20 patients who were successfully treated with laser trabeculoplasty as the primary therapy for glaucoma, we measured the intraocular pressure every two hours between 8:00 A.M. and 8:00 P.M. Success was defined as intraocular pressure of 22 mm Hg or less without medication. Of 20 patients, three had open-angle glaucoma and 17 had exfoliative glaucoma. Intraocular pressure was stable with small fluctuations during the daytime.

INTRAOCULAR PRESSURE can vary considerably in glaucomatous eyes.<sup>1-3</sup> Glaucoma surgery and antiglaucoma medication are reported to reduce the diurnal intraocular pressure variations in patients with glaucoma.<sup>4,5</sup> Greenidge, Spaeth, and Fiol-Silva<sup>6</sup> and Schwartz, Perman, and Whitten<sup>7</sup> investigated the effect of laser trabeculoplasty on the 24-hour diurnal pressure curve in patients with glaucoma already taking medication. We examined the effect of primary laser trabeculoplasty on the pressure curve from 8:00 A.M. to 8:00 P.M. without the influence of antiglaucoma medication.

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## Patients and Methods

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In October 1989, we completed a study on the long-term results of primary laser trabeculoplasty in 60 eyes of 60 patients with open-angle glaucoma or exfoliative glaucoma.<sup>8</sup> These patients were the subjects for the present study and were recruited from two earlier prospective

laser trabeculoplasty studies.<sup>9,10</sup> The patients had to fulfill the following criteria to enter these two studies: intraocular pressure of 25 mm Hg or greater on each reading of a 12-hour pressure curve (from 9:00 A.M. to 9:00 P.M.)<sup>9</sup> or of a nine-hour pressure curve (from 9:00 A.M. to 6:00 P.M.)<sup>10</sup> with pressure measurements every three hours; glaucomatous disk damage, glaucomatous visual field defects, or both (the definition of glaucomatous disk and visual field damage have been reported elsewhere<sup>8</sup>); and no earlier glaucoma medication. The laser trabeculoplasty was performed according to the method of Wise.<sup>11</sup> Success was defined as intraocular pressure of 22 mm Hg or less without medication.

The patients were followed up in January 1990. Of 60 patients, 28 were still considered to be successfully treated. Of these 28 patients, diurnal pressure studies were performed in 20 patients. Seven patients were not willing to participate in the study, and one patient had had a recent cerebral thrombosis, which made him unable to take part in the investigation. There were 17 patients with exfoliative glaucoma and three with open-angle glaucoma. The mean age was  $75 \pm 9$  years. There were six women and 14 men. The mean follow-up period was  $42 \pm 13$  months (range, 25 to 63 months).

Intraocular pressure was measured every two hours between 8:00 A.M. and 8:00 P.M. with a Goldmann applanation tonometer. The mean intraocular pressure (average of all pressure readings), mean square of intraindividual variation, and mean square of interindividual variation were calculated.

Two kinds of intraocular pressure variation were considered: variation for each individual during the day and variation between individuals. A one-way analysis of variance was applied to calculate the mean squares of these variations; the mean squares act as the variance estimates.<sup>12</sup> The mean square of intraindividual pressure variation is a measure of the fluctua-

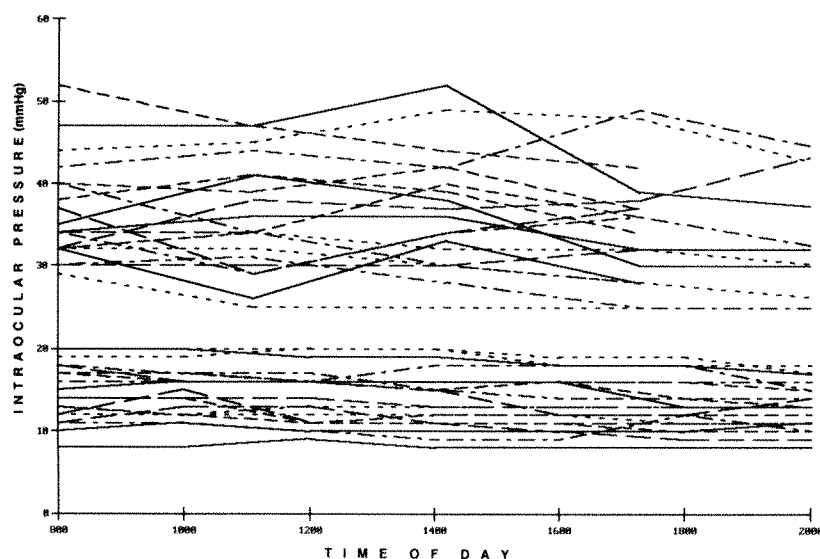
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**Figure** (Elsás, Junk, and Johnsen). Pressure curves before and after successful primary laser trabeculoplasty. Each curve, solid or dotted, represents the pressure readings of one single eye. The population is clearly divided into two groups, one below and one above the 20-mm Hg level. All treated eyes are below, whereas all untreated eyes are above the 20-mm Hg level.

tion around the mean pressure observed in every single eye and averaged over all eyes in the group. In this way all points of measurement are taken into consideration. In a similar manner, the mean square of interindividual variation is a measure of the fluctuation of the mean pressure in each eye around the mean pressure of the whole group. Bartlett's test was used to evaluate the homogeneity of variance within groups, and Fisher's F-test was used to test for equality of variance between different groups. A comparison of two mean values was carried out by Student's *t*-test.<sup>12</sup> For all tests, a *P* value of less than .05 was considered significant.

## Results

In pressure curves taken before and after successful primary laser trabeculoplasty, the population was clearly divided into two groups: one below the 20-mm Hg level and one above the 20-mm Hg level. All treated eyes were below this level, whereas all untreated eyes were above it (Figure).

The mean intraocular pressure was  $35.4 \pm 6.5$  mm Hg before treatment and  $13.9 \pm 3.3$  mm Hg after treatment. In addition to a reduction of the mean intraocular pressure, both intraindividual and interindividual pressure variations were reduced. These observations were confirmed by the statistical tests on the mean

square of the intraindividual and interindividual pressure variation (Table).

## Discussion

Our study shows that intraocular pressure was stable with small fluctuations during the daytime in patients who were successfully treated by primary laser trabeculoplasty. Intraindividual and interindividual pressure variations were significantly reduced. The normal physiologic pressure fluctuations during the daytime seemed to be abolished. Random pressure readings during office hours would have reflected the intraocular pressure during the

**TABLE**  
INTRAOCULAR PRESSURE VARIABLES BEFORE AND AFTER TREATMENT IN 20 PATIENTS SUCCESSFULLY TREATED WITH PRIMARY LASER TRABECULOPLASTY

	BEFORE TREATMENT	AFTER TREATMENT	P VALUE
Mean intraocular pressure (mmHg) $\pm$ S.D.	$35.4 \pm 6.5$	$13.9 \pm 3.3$	< .001
Intraindividual pressure variation (mean square)	11.58	1.36	< .001
Interindividual pressure variation (mean square)	161.28	61.47	.042

daytime in these patients. Greenidge, Spaeth, and Fiol-Silva<sup>6</sup> demonstrated a beneficial effect of laser trabeculoplasty on the diurnal curve of patients taking glaucoma medication. Schwartz, Perman, and Whitten<sup>7</sup> noted a 24-hour intraocular pressure-reducing effect after laser trabeculoplasty in patients with normal-tension glaucoma. We did not investigate the intraocular pressure during the nighttime. Peak intraocular pressures in patients with glaucoma not taking medication usually occur during the day.<sup>13</sup> Kitazawa and Horie<sup>3</sup> found that only four of 27 eyes (13%) of 14 patients with glaucoma not taking medication had peak intraocular pressures between 8:00 P.M. and 8:00 A.M.

We noted a large pressure reduction in this group of successfully treated patients. The mean pretreatment pressure was 35.4 mm Hg, which was reduced to 13.9 mm Hg after treatment. There seems to be a group of patients whose response to primary laser trabeculoplasty is a clinically large pressure reduction.

Primary laser trabeculoplasty is an inexpensive procedure with a low rate of complications. A multicenter study recently reported promising results with laser trabeculoplasty as initial therapy for open-angle glaucoma.<sup>13</sup> The stable intraocular pressure during the daytime in successfully treated patients is still another finding in favor of considering laser trabeculoplasty as the initial therapy for open-angle glaucoma.

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# Cytopathologic Diagnosis of Benign Lesions Simulating Choroidal Melanomas

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Devron H. Char, M.D., Theodore R. Miller, M.D., and J. Brooks Crawford, M.D.

In three cases of benign pigmented lesions (one melanocytoma and two pigment epithelial adenomas) there was evidence of tumor growth and the lesions were referred to us as uveal melanomas. The fine needle aspiration biopsy specimens were correctly interpreted in the operating room as being benign tumors. The pigment granules in these benign pigmented lesions are much larger than are observed in uveal melanomas. When they were visible through the heavy pigmentation, the cellular detail appeared benign. In two cases the tumors were successfully resected with cyclochoroidectomy techniques and the visual outcome was good. The third eye was studied after it had been removed at another institution. Fine needle aspiration biopsy can often differentiate a benign-simulating pigmented lesion from uveal melanoma.

**F**INE NEEDLE ASPIRATION biopsy has been used to diagnose a number of intraocular tumors including lymphoma, uveal melanoma, retinoblastoma, and metastases.<sup>1-5</sup> Little data exist concerning its diagnostic accuracy for nonmalignant intraocular masses, although a few cases of false-positive results have been reported.<sup>6</sup>

Diagnosis of anterior intraocular tumors is often difficult.<sup>7</sup> The ultrasonographic pattern of lesions in this location is not as diagnostic as in

the posterior pole, and fluorescein angiography has limited use for anterior choroid and ciliary body tumors.<sup>8,9</sup> We studied three cases of benign pigmented proliferations that had a sufficiently characteristic fine needle aspiration biopsy pattern to differentiate them in the operating room from uveal melanoma before resection of the lesions.

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## Case Reports

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### Case 1

A 57-year-old white woman was referred for treatment of a growing, right ciliary body tumor. The patient had the presumed ocular histoplasmosis syndrome and decreased vision in the right eye after argon laser to a macular subretinal neovascular membrane. In January 1987, she developed recurrent decreased vision in the right eye. Iritis occurred. With topical corticosteroids visual acuity returned to 20/20. Visual acuity diminished again, and a cataract and a ciliary body mass were noted in the right eye. The patient was referred to us for further examination.

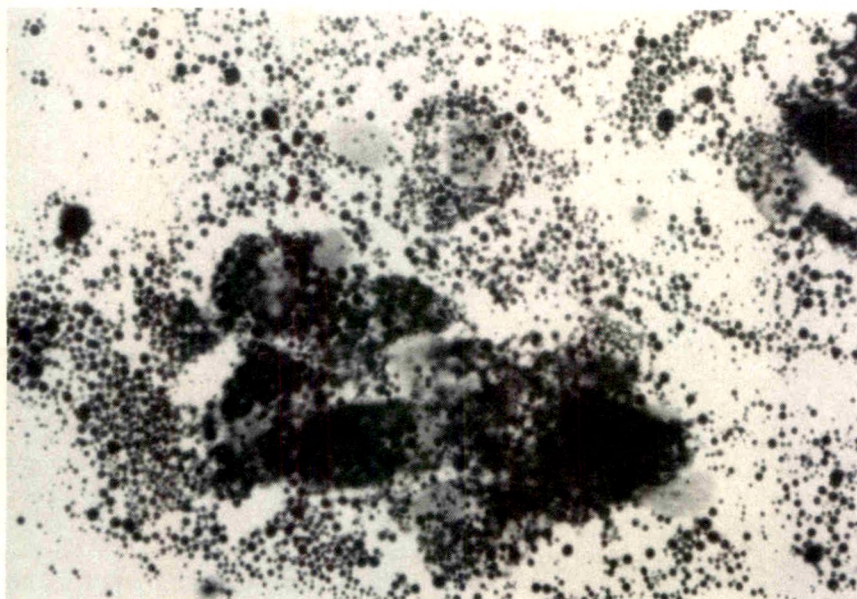
At our examination, best-corrected visual acuity was R.E.: 20/80 and L.E.: 20/20. The right anterior segment had a sentinel vessel in the area of the tumor, and there were mild cell and moderate flare in the anterior chamber. The right iris was bowed forward between the 12 and 2 o'clock meridians with a posterior synechia at 12:30; there was sector cataract in that area. On contact lens examination the angle appeared to be open and there was a mass that blocked transillumination. It was brown and approximately one clock hour diameter with a maximum thickness, clinically and on ultrasonography, of 5.4 mm. Ultrasound was consistent with a ciliochoroidal melanoma. The intraocular pressure was 15 mm Hg bilaterally, and both fundi showed inactive presumed ocular histoplasmosis.

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**Fig. 1** (Char, Miller, and Crawford). Cytopathology of a pigmented epithelial adenoma. Note the large pigment granules. Uveal melanomas are not associated with pigment granules of this size (May-Giemsa-Grunewald,  $\times 40$ ).

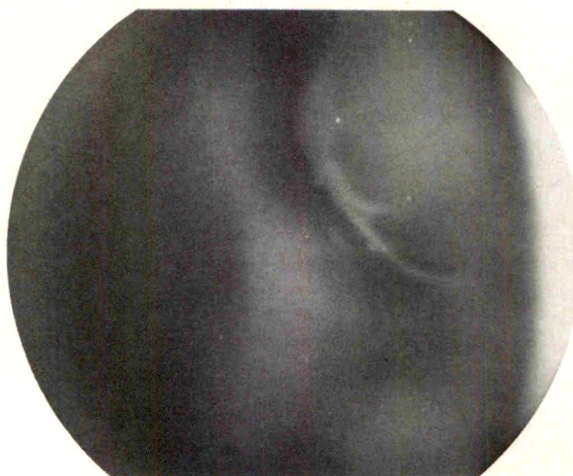
The patient was taken to the operating room for a cyclochoroidectomy of this lesion because of the history of growth. A 90% thickness scleral flap was dissected over the area of the tumor. A fine needle aspiration biopsy was performed through the resection site, and showed very large pigment granules and benign appearing cells (Fig. 1). Our impression in the operating room of the cytology rapid stain was that this was a benign pigmented neoplasm. The final cytology preparation with Papanicolaou and May-Giemsa-Grunewald stains confirmed the intraoperative impression. The tumor cells occurred both in cohesive clusters and as single cells. Cells had an abundant amount of cytoplasm with a slightly polygonal shape. Within the cytoplasm were numerous spherical pigment granules that were brown. The granules were slightly refractile. Because of cell disruption, the background contained numerous spherical pigment granules that varied somewhat in size, but very little in shape. Microscopic examination of the resected tumor showed a well-circumscribed, highly pigmented tumor originating from the pigmented ciliary epithelium. Tubules of pigmented epithelium are separated by eosinophilic septae with fine blood vessels. The cells were well-differentiated pigment epithelial cells with large pigment granules and no significant cellular atypia. It was a benign adenoma of the pigmented ciliary epithelium.

Postoperatively the patient did well. On her last visit, approximately one year later, her visual acuity was 20/25.

## Case 2

A 50-year-old white woman was referred because of a growing left ciliochoroidal tumor. The patient had noted decreased vision in her left eye approximately six weeks before our examination. She had had no previous ophthalmologic care. She was found to have a ciliochoroidal tumor, and serial examinations by another physician showed growth (Fig. 2). The patient was referred for evaluation and therapy.

On examination the visual acuity was 20/70 in the involved eye. Intraocular pressure was normal. There was anterior displacement of the iris between 8:30 and 10:00 o'clock meridians



**Fig. 2** (Char, Miller, and Crawford). A peripheral presumed pigmented ciliochoroidal melanoma with a history of growth.



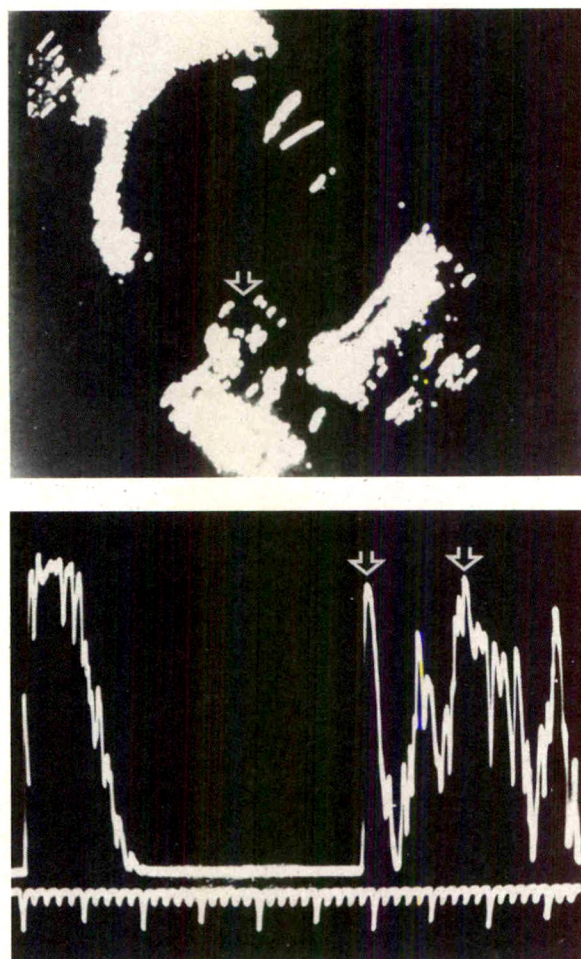


Fig. 3 (Char, Miller, and Crawford). Top, B-scan demonstrates an anterior mass with acoustical quiet zone (large arrow); bottom, standardized A-scan demonstrates a large mass (arrows).

and some distortion of the peripheral iris with a 2-mm area of breakthrough of this deeply pigmented lesion. There was no evidence of anterior chamber inflammation. The lesion was bilobed and encompassed the edge of the lens between its lobes. It was uniformly dark in color, and blocked transillumination. An ultrasound showed a mass with a maximum thickness of 6.1 mm. The pattern on A- and B-scans was consistent with an anterior uveal melanoma (Fig. 3).

The patient was taken to the operating room and a 90% scleral flap was created. A fine needle aspiration biopsy showed a benign lesion with large pigment granules consistent with either a melanocytoma or a benign retinal pigment epithelial tumor. Permanent cytology slides stained with May-Giemsa-Grunewald and Papanicolaou stain demonstrated clusters

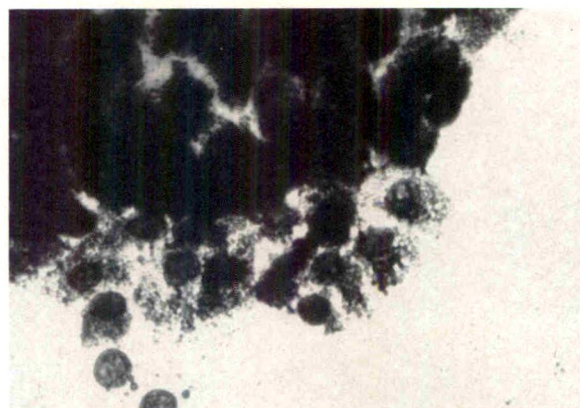


Fig. 4 (Char, Miller, and Crawford). Cytopathology demonstrates a retinal pigment epithelium adenoma with large pigment granules (Papanicolaou,  $\times 40$ ).

and single tumor cells. The tumor cells were characterized by a slightly polygonal shape and abundant cytoplasm. Within the cytoplasm were spherical refractile brown granules that varied only slightly in size (Fig. 4). The nuclei were round to oval and unremarkable, without evident nuclei. The granules showed a refractile quality when the condenser light was lowered. Many of the cells had been disrupted and the refractile granules were scattered throughout the background.

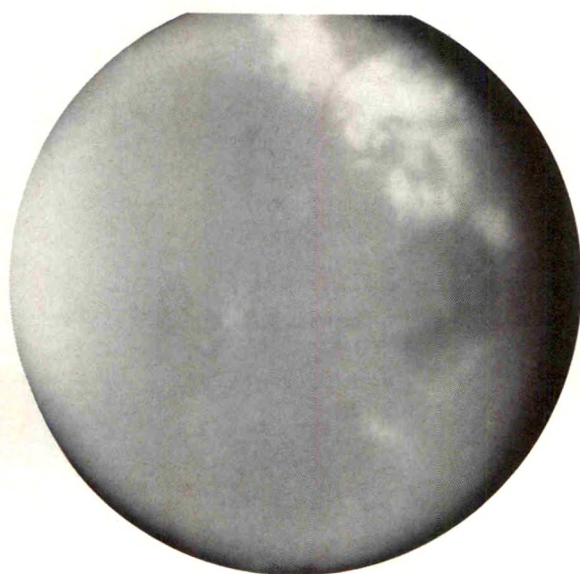
The lesion was resected with good margins. Microscopic examination showed a melanocytoma of the ciliary body that extended into the root of the iris. The individual cells had small, benign-appearing nuclei and abundant cytoplasm that was heavily pigmented with melanin granules of various sizes.

Postoperatively the patient's visual acuity returned to 20/40.

### Case 3

A 73-year-old white woman was referred because of pigmented choroidal mass at the nasal equator of her right eye. Approximately ten years previously there had been surgical placement of an encircling element to treat a rhegmatogenous detachment. The mass was first noted approximately one year before our examination and growth was observed on serial observation. The patient's visual acuity was 20/80. The involved eye had moderate old vitreous cell and debris. Approximately 9 mm nasal to the disk was a pigmented mass that was  $6 \times 6 \times 4.5$  mm in size (Fig. 5). There was retinal pigment epithelial hyperplasia on its surface. A circumferential buckle was just anterior to the mass. An ultrasound was not consis-





**Fig. 5** (Char, Miller, and Crawford). Equator-plus camera photograph of a pigmented lesion in an area of previous retinal detachment surgery with documented growth.

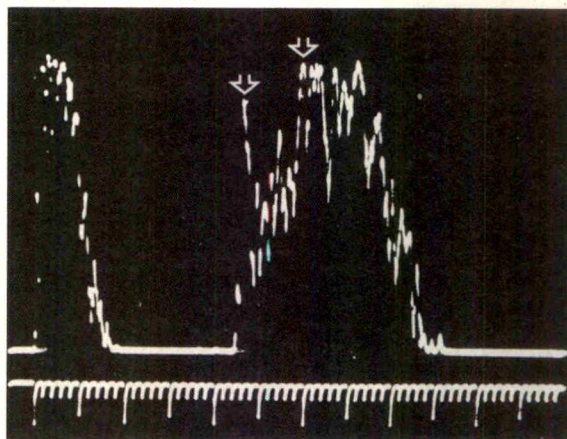
tent with a uveal melanoma. On standardized A-scan the pattern was relatively heterogeneous with coarse spikes (Fig. 6).

On serial evaluation the tumor demonstrated growth and on ultrasound showed possible scleral extension. A fine needle aspiration biopsy was performed and was consistent with a benign pigmented lesion. Large pigment granules were observed and the cells appeared to be benign.

Approximately five years later the patient developed a painful eye and it was removed by another physician. Microscopic examination showed a black tumor in an area under the encircling synthetic band. This corresponded to a focal area of retinal pigment epithelial hyperplasia, forming a nodule. The individual cells showed loss of polarity but no significant pleomorphism. Necrotic cells were located on the apex of this nodule.

### Discussion

Many researchers have demonstrated the accuracy of fine needle aspiration biopsy diagnosis of uveal melanoma.<sup>2,5,7,10,11</sup> We have had no false-positive results in over 100 melanomas.<sup>11</sup> It is often difficult to make the correct diagnosis of pigmented anterior choroidal and ciliary



**Fig. 6** (Char, Miller, and Crawford). Standardized A-scan demonstrates a heterogeneous lesion (arrows).

body tumors. Melanocytoma, primary proliferations of the pigment epithelium, and less common entities that result in secondary pigment epithelial hyperplasia are often incorrectly diagnosed, especially in these locations. In some cyclochoroidectomy series a false-positive melanoma diagnosis has been reported in as many as 40% of such anterior cases.<sup>7,8</sup> In atypical nonmelanomatous pigmented lesions, the accuracy of fine needle aspiration biopsy is uncertain.<sup>6</sup> In this study we have differentiated one melanocytoma and two pigment epithelial adenomas from malignant melanoma.

Large, uniformly spherical pigment granules were the most useful finding on cytopathologic fast stain to differentiate benign pigmented lesions from uveal melanomas. These granules were noted to have a refractile quality in low illumination. We have never observed granules of this size or quality in uveal melanomas. Cells visible through the dark pigmentation also had a uniform appearance with normal nuclear to cytoplasmic ratios; however, in one case the amount of pigment made it difficult to analyze cellular detail in the operating room. These cells lacked nucleoli as compared to epithelioid melanoma cells that can have the same general cell shape.

Melanocytomas can occur in the ciliary body, iris, sclera, conjunctiva, choroid, and optic nerve, although less than 15 ciliary body melanocytomas have been reported.<sup>12-24</sup> Slow growth has been documented in a number of cases.<sup>12-17</sup> Most eyes with anterior melanocytomas have been enucleated with a clinical diagnosis of a uveal melanoma.<sup>18-24</sup> Usually the tumor is deep-



ly pigmented and often a sector cataract is present; unfortunately these characteristics do not always differentiate these neoplasms from melanomas. In some melanocytomas, ultrasonography will have a pattern similar to that in Case 3. However, in other melanocytomas we have resected, the ultrasonographic pattern was consistent with a melanoma. As shown in Case 2, we could correctly differentiate this benign pigmented lesion from a melanoma on fine needle aspiration biopsy, although the differentiation between a melanocytoma and a retinal pigment epithelium proliferation was not possible.

Many events can cause retinal pigment epithelium proliferation.<sup>25,26</sup> Rarely an amelanotic tumor will induce overlying proliferation of the retinal pigment epithelium that simulates the color of a pigmented uveal melanoma.<sup>8,27</sup> We reported such a case of metastatic carcinoid that was diagnosed by fine needle aspiration biopsy.<sup>8</sup> Primary proliferations of the pigment epithelium can produce large lesions, as in Cases 1 and 3. These primary pigment epithelial tumors can be misdiagnosed as a uveal melanoma.<sup>25,28,29</sup> The cytopathologic features observed in our cases should be sufficient to differentiate these processes from a malignancy and avoid enucleation. In Case 3, the result of fine needle aspiration biopsy was consistent with either a retinal pigment epithelial process or a melanocytoma, and we continued to observe the patient despite documented enlargement. Several years later the eye became painful and our diagnosis was confirmed histologically. In the two predominantly ciliary body lesions, the history of growth in Case 2, and our observation of growth in Case 1, led us to remove each lesion with consequent retention of a useful eye.

Theoretic questions have been raised about the safety of fine needle aspiration biopsy for intraocular tumors.<sup>30,31</sup> We have not had any major complications or evidence of tumor spread in over 200 cases of intraocular or orbital fine needle biopsies dating back to the mid-1970s.<sup>7</sup> We are unaware of any evidence of either local growth in a needle tract or distant spread when a 25-gauge or smaller bore needle has been used.<sup>7</sup> While serial sections can show a few tumor cells in the needle tract, probably the numbers of such neoplastic cells are too few to develop viable colonies.<sup>31</sup> We routinely obtain a fine needle aspiration biopsy in any lesion that requires therapy where noninvasive diagnostic techniques are equivocal. In each of these three

lesions referred with the diagnosis of a probable uveal melanoma, the correct diagnosis was established with fine needle aspiration biopsy.

More information can probably be obtained from fine needle aspiration biopsies than is routinely done at present. In other investigations we have demonstrated that cytomorphometric, DNA content, and cell cycling analysis with bromodeoxyuridine can be assessed on this material.<sup>11</sup> Several investigators have demonstrated that immunohistochemistry, electron microscopy, in situ hybridization, and tissue culture studies can also be performed on cytopathology specimens.<sup>32,33</sup>

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#### OPHTHALMIC MINIATURE

When he first thought about him it was always the eyes. The big frame, the quick movements, the wide shoulders, the hooked, hawk nose, the beard that covered the weak chin, you never thought about—it was always the eyes. They were protected in his head by the formation of the brows, set deep as though a special protection had been devised for some very valuable instrument. They saw much further and much quicker than the human eye sees and they were the great gift his father had. His father saw as a bighorn ram or as an eagle sees, literally.

Ernest Hemingway, *The Nick Adams Stories*  
New York, Charles Scribner's Sons, 1972, p. 257



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# Intrathecal Antibody Production Against Viruses of the Herpesvirus Family in Acute Retinal Necrosis Syndrome

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and Marianne Forsgren, M.D.

Viruses of the herpesvirus family cause acute retinal necrosis syndrome, a devastating necrotic retinitis in immunocompetent individuals. Direct proof of the viral origin of this disease may be obtained by demonstration of the virus, viral antigens, or viral DNA in biopsy specimens of retinas. In search of alternative diagnostic methods, we analyzed cerebrospinal fluid and serum with enzyme-linked immunosorbent assays for virus-specific antibody activity. Intrathecally produced viral antibodies were found in three consecutive patients with acute retinal necrosis syndrome: herpes simplex type 2 in a 30-year-old woman with a history of suspected neonatal herpes encephalitis, herpes simplex type 1 in a 35-year-old man, and varicella-zoster virus activity in a 62-year-old woman. None of the patients had clinical signs indicating an acute disorder in the central nervous system. This serologic approach seems to be of value for the diagnosis of an associated intracerebral viral infection in cases of acute retinal necrosis syndrome.

**C**LINICAL RECOGNITION of the acute retinal necrosis syndrome is currently based on typical ophthalmic appearance and case history. Detection of virus-specific antibodies in the aqueous humor has been helpful to corroborate presumed origin,<sup>1-8</sup> whereas determination of

serum antibodies has proven to be futile. Lewis and associates<sup>9</sup> demonstrated that cerebral involvement may be present. Results from previous serologic investigations of the cerebrospinal fluid and blood have been inconclusive. Careful selection of modern serologic methods has made possible more accurate analysis of cerebrospinal fluid, serum activity, and intrathecal antibody production, which is an indicator of infection of the brain with herpes simplex<sup>10-15</sup> or varicella-zoster virus.<sup>11,16</sup> By analysis with the enzymelinked immunosorbent assay of class- and subclass-specific antibody activity in simultaneously obtained samples of cerebrospinal fluid and serum from three consecutive patients with acute retinal necrosis syndrome, we found intrathecal antibody production, which probably suggested a concurrent infection in the central nervous system: one of herpes simplex virus types 1 and 2, respectively, and one of varicella-zoster virus.

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## Patients and Methods

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We studied three consecutive patients with acute retinal necrosis syndrome who were examined between 1986 and 1989 at the Department of Ophthalmology at Huddinge University Hospital (population basis, 300,000).

Cerebrospinal fluid and serum samples, obtained simultaneously in the acute phase and at the follow-up examination, were analyzed for IgG antibody activity against viral antigen from influenza A, mumps, herpes simplex, varicella-zoster, measles, and cytomegalovirus. The samples were examined with indirect ELISA<sup>13</sup> in four tenfold dilutions starting at 1:10 for the cerebrospinal fluid and at 1:100 for the serum. The results indicated intrathecal synthesis of herpes simplex antibodies in two patients (Cases 1 and 2) and varicella-zoster antibodies in one patient (Case 3). These preliminary diag-

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noses were followed up by analyses of the samples with ELISA testing.

**Class- or subclass-specific activity**—The IgG, IgA, and IgM class-specific antibody activities were analyzed with indirect ELISA<sup>13</sup> in fourfold dilutions starting from 1:12.5 and 1:50, respectively, for cerebrospinal fluid and serum. Activities against herpes simplex type common<sup>13</sup> and varicella-zoster antigens<sup>11</sup> were assayed, and against herpes simplex type 2-specific glycoprotein antigen<sup>17</sup> in Cases 1 and 2 as well. The patient sample was added to the viral antigen, which was attached to a solid phase (microtiter plates). During incubation the viral antibody, if present in the sample, was bound to the antigen. After washing, in a second incubation the bound virus-specific antibody from the patient was reacted with a class-specific or antiglobulin antibody (Dakopatts, Copenhagen, Denmark) conjugated with the enzyme alkaline phosphatase. The conjugate was immunologically bound if virus-specific antibodies of the indicated class were present. The amount of enzyme was quantified in a color reaction with an enzyme substrate (p-nitrophenylphosphate). The intensity of the color, the absorbance value at 405 nm, was a measure of the absolute amount of antibody activity that was present in the analyzed sample. A concurrent damage of the blood-brain barrier, with increased passage of serum activity into the cerebrospinal fluid, affected the results. Therefore, the ratio between herpesvirus activity in the cerebrospinal fluid and serum was compared to a corresponding ratio of a reference antibody, measles, to evaluate the intrathecal antibody production. Thus, all dilutions of the cerebrospinal fluid and serum were also simultaneously analyzed for measles activity. A fourfold higher cerebrospinal fluid:serum ratio of the herpes simplex virus antibody, compared to that of anti-measles, indicated intrathecal antibody production.<sup>13</sup>

IgG subclass virus-specific activity<sup>12,16</sup> was analyzed with similar indirect ELISA testing. After incubation of the patient samples with the antigen, dilutions of mouse monoclonal human IgG subclass 1 to 4 specific antibodies were added (anti-IgG clone HP 6014, Center for Disease Control, Atlanta, Georgia; anti-IgG 1, 3, 4, Searl's Laboratories, London, United Kingdom). Horseradish peroxidase labeled rabbit antimouse IgG (Dakopatts, Copenhagen, Denmark) was used as conjugate. The color reaction with ortho-phenylenediamine was read at 490-nm optical density.

**Enzyme-linked immunosorbent assay**<sup>14</sup>—The patient samples of cerebrospinal fluid and serum, diluted 1:10 and 1:1,000 or 1:100 and 1:10,000, respectively, were added to microtiter plates coated with rabbit antihuman IgG. During incubation a constant amount of IgG antibodies in the patient sample was immunologically bound to the IgG antibodies. Herpes simplex antigen was added after washing. If herpes-specific antibodies were present in the sample, herpes antigen bound proportionally to the amount of this antibody. During the next incubation, bound herpesvirus antigen was reacted with rabbit antiherpes simplex virus F(ab)<sub>2</sub> fragments labeled with horseradish peroxidase. The optical density at 490 nm of the color of the substrate reaction with ortho-phenylenediamine was proportional to the initial amount of herpes-specific IgG bound to the cerebrospinal fluid or serum sample. Because the amount of the total IgG that was bound to the patient sample was constant, the intensity of the final color reaction reflected the proportion of herpes-specific IgG antibody activity present in the patient sample. This proportion was not affected by a disturbance of the blood-brain barrier. Thus, the color reactions of the cerebrospinal fluid and serum were normally equal. Intrathecal antibody production, however, resulted in an increased proportion of herpes-specific IgG in the cerebrospinal fluid, and consequently, the color intensity of the cerebrospinal fluid was higher than that of the serum. For interpretation of the results the difference between the absorbance values of the cerebrospinal fluid and serum were compared to a cut-off indicator included in each test. Values exceeding the cut-off indicator indicated intrathecal antibody production. The cut-off indicator was standardized against a large panel of reference samples.<sup>14</sup> A similar assay was used for varicella-zoster virus IgG antibodies. For detection of virus-specific IgM activity, the first binding antibody was rabbit anti- $\mu$ -chain immunoglobulin. Otherwise, the procedure was identical.

## Results

### Case 1

A 35-year-old man had blurred vision and pain in the right eye for one week. At 19 years of age, the patient had had a mild papillitis in his right eye. Anterior uveitis, vitreitis, and papillitis were found. The left eye was uninvolved.



Oral prednisolone (60 mg daily) was given. Signs of inflammation regressed, but visual acuity deteriorated to 20/200. Exudative white retinal lesions, which initially involved the temporal periphery, progressed to include the entire circumference of the peripheral retina. Arteritis of the retinal vessels developed during the next three weeks. The lesions were characteristic of acute retinal necrosis. Acyclovir (1 g three times daily) was given intravenously for ten days and continued orally (200 mg three times daily) for three months. The necrotic lesions resolved rapidly, whereas the arteritis regressed more slowly. A mild vitreitis remained after six months. No further retinal complications developed. There were no clinical symptoms of involvement of the central nervous system and no herpetic lesions.

The cerebrospinal fluid was examined twice: in the acute phase and four months after onset of ocular symptoms. Tests for syphilis, *Borrelia* species, and malignant cells were negative, as were cultures for virus and bacteria. The cerebrospinal fluid:serum albumin ratio was normal. The IgG index became slightly increased during the time of observation (4.5 months). The blood cell counts of the cerebrospinal fluid were normal. The immunoelectrophoresis of the cerebrospinal fluid showed oligoclonal bands in the IgG fraction not present in the serum pattern, which was normal (Table 1). The serologic survey of the cerebrospinal fluid and serum showed no signs of intrathecal antibody production to varicella, cytomegalovirus, measles, influenza A, and adenovirus. Both indirect and capture ELISA testing disclosed intrathecal synthesis of antibodies to herpes simplex type common antigen of IgG but not of IgM (Table 2). Analysis of the herpes simplex virus subclass antibody activity disclosed intrathecal production of Ig3 and Ig4. Antibodies to herpes type 2-specific antigen were not detectable in the cerebrospinal fluid or serum.

## Case 2

A 30-year-old mentally retarded woman had relapsing uveitis with persistent vitreitis in her left eye for six years. The origin of this condition had not been established, and the cerebrospinal fluid had not been examined. She had been treated with high doses of oral prednisolone twice, without improvement. At the age of 30 years, after a nasal sinusitis, a non-granulomatous iritis developed in the right eye. The iritis was shortly followed by the onset of retinal arteritis and peripheral retinal necrosis

**TABLE 1**  
NONSEROLOGIC FINDINGS IN THE CEREBROSPINAL FLUID IN ACUTE RETINAL NECROSIS SYNDROME

SAMPLING TIME AFTER ONSET OF NECROTIC CHANGES	CELL COUNT		OLIGOCLONAL BANDING IN	
	MONONUCLEAR LYMPHOCYTES (CELLS/L)	ALBUMIN RATIO*	IgG INDEX†	IMMUNOELEC- TROPHORESIS
<b>Case 1</b>				
3 weeks	$4.0 \times 10^6$	$3.8 \times 10^{-3}$	0.6	Strong
4.5 months	$4.7 \times 10^6$	$4.0 \times 10^{-3}$	0.8	Strong
<b>Case 2</b>				
2 days	$7.7 \times 10^6$	$3.7 \times 10^{-3}$	2.8	Intense
3 months	$2.8 \times 10^6$	$4.6 \times 10^{-3}$	1.7	Intense
8 months	$6.6 \times 10^6$	$3.7 \times 10^{-3}$	2.7	Intense
<b>Case 3</b>				
8 days	$5.5 \times 10^6$	$5.7 \times 10^{-3}$	0.6	Weak
1 month	$4.4 \times 10^6$	$4.8 \times 10^{-3}$	0.7	Strong
4 months	$1.4 \times 10^6$	$5.9 \times 10^{-3}$	0.6	Intense

\*Albumin ratio is the ratio of albumin levels in cerebrospinal fluid serum, normal  $< 10 \times 10^{-3}$

†IgG index is the IgG ratio of cerebrospinal fluid: serum to albumin ratio of cerebrospinal fluid: serum, normal  $< 0.7$ .

in the right eye and worsening of the persistent vitreitis in the left eye. Acyclovir (600 mg three times daily) was administered intravenously and salicylate (2 g per day) was given orally for ten days. The necrotic lesions subsided.

Within the next month a severe vitreitis developed in the right eye, despite oral prednisolone (40 mg per day) and continued acyclovir treatment. The retina became detached in the right eye after another month. Attempts at repair (vitrectomy, retinotomy, and injection of silicone oil) were unsuccessful. The patient had no clinical signs of acute neurologic disorder and no serologic signs of immunodeficiency, syphilis, toxoplasmosis, or bacterial infections. A facial x-ray disclosed slight mucosal thickening in the left maxillary sinus. Repeated examinations of the cerebrospinal fluid were performed at and after diagnosis of acute retinal necrosis syndrome. The cerebrospinal fluid:serum albumin ratios were normal. In the acute phase an increased IgG index (2.8) and a mononuclear pleocytosis ( $7.7 \times 10^6$  cells/l) were found, both of which declined transiently during the first months (Table 1). The immunoelectrophoresis of the cerebrospinal fluid, but not of the serum, showed oligoclonal bands in the IgG fraction, which persisted after the acute phase. The initial screening tests for intrathecal viral antibody production were positive for herpes-

**TABLE 2**  
**ANTIBODY ACTIVITY TO HERPES SIMPLEX VIRUS VARICELLA-ZOSTER, AND MEASLES IN CEREBROSPINAL FLUID AND SERUM SAMPLES WITH TWO DIFFERENT ENZYME-LINKED IMMUNOSORBENT TECHNIQUES IN CASES 1 AND 2**

SAMPLING TIME AFTER ONSET OF NECROTIC CHANGES	INDIRECT ELISA TITER				$\gamma$ -CAPTURE ELISA
	HERPES SIMPLEX		VARICELLA- ZOSTER	MEASLES	ABSORBANCE VALUE OF HERPES SIMPLEX TYPE COMMON
	TYPE COMMON	TYPE 2 SPECIFIC			
Case 1					
3 weeks					
Cerebrospinal fluid	800*	< 12.5	< 12.5	< 12.5	2.33*
Serum	12,800	< 50	1,600	1,600	0.90
4.5 months					
Cerebrospinal fluid	400*	NP†	< 12.5	< 12.5	2.38*
Serum	25,600	< 200	1,600	3,200	0.75
Case 2					
2 days					
Cerebrospinal fluid	6,400*	100*	< 12.5	< 12.5	2.25*
Serum	102,400	1,600	1,600	800	0.79
3 months					
Cerebrospinal fluid	3,200*	50*	< 12.5	< 12.5	2.03*
Serum	51,200	800	1,600	1,600	0.01
8 months					
Cerebrospinal fluid	6,400*	100*	< 12.5	< 12.5	2.22*
Serum	102,400	800	1,600	1,600	0.65

\*Intrathecal antibody production.

†NP indicates not performed.

virus activity only. Antivaricella-zoster virus and cytomegalovirus activity in the cerebrospinal fluid were barely detectable, which made an infection with either of these viruses unlikely. Repeated analyses with indirect ELISA confirmed a significantly higher intrathecal production to herpes type common and herpes type 2 antibody (Table 2). Herpes-specific IgA and IgM activity was not found in any sample. Analysis with capture ELISA corroborated the findings of intrathecal production of herpes simplex virus IgG. Subclass analysis disclosed herpes simplex virus-specific intrathecal antibody production of IgG1 and IgG3 classes. Herpes simplex virus IgG2 and IgG4 activity was not found. During the three months after the acute phase, the total herpes simplex-specific activity decreased but increased later (Table 2). These findings led us to examine the patient's records from the neonatal period. At 1 month of age the patient had had hemorrhagic encephalitis and vesicular skin eruptions. The electroencephalogram disclosed frontotemporal changes. There had been no attempts to establish the viral diagnosis during the postnatal period or later.

### Case 3

A 62-year-old woman, who had hypertension, angina pectoris, and sequelae from a recent myocardial infarction, was examined for a two-day history of blurred vision in her left eye. She had noticed a subtle numbness of her left cheek during the preceding month. She had a history of varicella during childhood and a right-sided thoracic herpes zoster infection eight years previously. During the next four weeks a severe retinal arteritis was followed by the development of extensive necrotic lesions in the peripheral retina in the left eye. The patient was treated with intravenous acyclovir (350 mg three times daily) for ten days, warfarin, and oral prednisolone (40 mg three times daily). While the necrotizing changes were healing, a fulminant vitreitis developed that resulted in retinal detachment within a month.

Vitreoretinal surgery was not performed because of the fragile cardiovascular status of the patient. The electroretinogram was extinguished in the left eye and was normal in the right eye. The fluorescein angiogram showed total occlusion of the peripheral vessels as well as extensive retinal necrosis. Laboratory tests



and x-ray examination disclosed no signs of immunodeficiency, syphilis, toxoplasmosis, sarcoidosis, tuberculosis, bacterial infections, and collagenous or inflammatory vascular disease. Neurologic status examination and results of the electroencephalogram were normal. The cerebrospinal fluid was sampled on three occasions; viral, bacterial, and fungal cultures were negative, and malignant cells were not found. The albumin ratios and IgG index were normal. An initial slight mononuclear pleocytosis ( $5.5 \times 10^6$  cells/l) subsequently declined (Table 1). In the IgG fraction of the immunoelectrophoresis of the cerebrospinal fluid, which was initially normal, multiple oligoclonal bands became evident with time, whereas the serum pattern remained normal. The initial serologic survey demonstrated intrathecal production of varicella-zoster IgG antibodies but not of other viral antibodies. Further analyses with indirect and capture ELISA confirmed this finding (Table 3). High-level, varicella-zoster virus-specific IgA activity (titer, 2,800) was present in serum but not in cerebrospinal fluid. Varicella-zoster virus-specific IgM was not found in any sample. Analyses of subclasses IgG1 to IgG4 reactive

with varicella-zoster virus disclosed a high level of activity of IgG3 in the cerebrospinal fluid and serum. The levels of antibodies to cytomegalovirus in the cerebrospinal fluid did not indicate intrathecal antibody production.

## Discussion

Usually, clinical signs of acute disorder of the central nervous system are absent in immunocompetent patients with acute retinal necrosis syndrome, as in our three patients. Obvious manifestations of intracranial involvement, such as visual field defects, hemiplegia, and meningoencephalitis, have been reported infrequently.<sup>9,16</sup> Inflammatory changes in the optic tracts and the lateral geniculate ganglia have been visualized by magnetic resonance imaging.<sup>9</sup> Previous serologic examinations of the cerebrospinal fluid have not been able to disclose an infection of the central nervous system in conjunction with acute retinal necrosis syndrome.<sup>18-22</sup> However, the observation of pleocytosis, typically mononuclear lymphocytosis, in this and previous studies<sup>9,23-27</sup> indicates a concomitant process in the central nervous system. Furthermore, the presence and persistence of oligoclonal bands in the electrophoretic patterns of the cerebrospinal fluid,<sup>28</sup> but not of the serum, were indicative of an immunoreaction within the central nervous system in our patients. In search for the specificity of the intrathecal antibodies, we used sensitive ELISA testing against a number of viruses, including herpes simplex and varicella-zoster. These techniques have been applied extensively to the serodiagnosis of encephalitis of herpes simplex and varicella-zoster origin and have been reliable.<sup>10-17</sup> Recent data demonstrated complete correspondence between the serodiagnoses and the results of the analysis of herpes DNA in the cerebrospinal fluid of a large number of patients with acute encephalitis of herpes simplex or other origin.<sup>15</sup>

The serologic analyses of the cerebrospinal fluid and serum from our patients disclosed intrathecally produced antibodies, the specificity of which suggested a different virus infection in the central nervous system in each of the three patients: herpes simplex type 1, type 2, and varicella-zoster, respectively. Additionally, intrathecal production of varicella-zoster antibodies was recently found in samples from a fourth patient. The finding of intrathecally

**TABLE 3**  
ANTIBODY ACTIVITY TO HERPES SIMPLEX VIRUS,  
VARICELLA-ZOSTER, AND MEASLES IN  
CEREBROSPINAL FLUID AND SERUM SAMPLES WITH  
TWO DIFFERENT ENZYME-LINKED IMMUNOSORBENT  
TECHNIQUES IN CASE 3.

	INDIRECT ELISA TITER			$\gamma$ -CAPTURE ELISA
SAMPLING TIME AFTER ONSET OF NECROTIC CHANGES	VARICELLA ZOSTER	HERPES SIMPLEX TYPE COMMON	MEASLES	ABSORBANCE VALUE OF VARICELLA ZOSTER
8 days				
Cerebrospinal				
fluid	400*	50	< 12.5	NP†
Serum	25,600	51,200	3,200	NP
1 month				
Cerebrospinal				
fluid	400*	50	< 12.5	1.84*
Serum	25,600	51,200	3,200	0.46
4 months				
Cerebrospinal				
fluid	NP	NP	NP	1.68*
Serum	NP	NP	NP	0.47

\*Intrathecal antibody production.

†NP indicates not performed.

produced subclass IgG3 antibody activity directed against the infecting virus suggested ongoing or recent virus replication, since such activity to varicella-zoster virus usually was not found in healthy, varicella-zoster antibody-positive individuals.<sup>13</sup> Herpes simplex virus IgG3 is rarely detected in the cerebrospinal fluid of healthy individuals but may be frequently present in serum.<sup>28</sup> Intrathecal production of herpes simplex- and varicella-zoster-specific antibodies are seldom found in neurologically healthy persons. Furthermore, varicella-zoster and herpes simplex viruses are proven etiologic agents in acute retinal necrosis syndrome.<sup>9,18</sup> Thus, an association between the serologically indicated intracerebral infection with a herpesvirus and the ocular disease in each of the three consecutive patients is likely.

In our three cases, intracerebral involvement seemed to have preceded the retinitis, because the antibody level in the cerebrospinal fluid was maximal already at the onset of the retinal disease. Furthermore, the absence of virus-specific IgM activity in the cerebrospinal fluid was not suggestive of a primary infection. It is possible that the previous mild papillitis in one patient (Case 1) may have been caused by herpesvirus type 1. One patient (Case 2) had a compelling history of neonatal herpes encephalitis, which led to the devastating late ocular sequelae. The intrathecal antibody synthesis, present already at the onset of the acute retinal necrosis in her right eye, was followed by a transient decline. One might speculate that the exacerbation of the retinitis could have been the result of an otherwise asymptomatic reactivation of her persistent intracerebral infection. The fluctuations of cell content, IgG index, and herpes antibody activity in the cerebrospinal fluid at the follow-up examination may reflect variability of activity of her intracerebral infection. Although no direct evidence for the intraocular virus was available, the findings in this case suggest a link between herpesvirus type 2 infection and the acute retinal necrosis syndrome.<sup>29</sup> One patient (Case 3) had an antecedent history of a varicella-zoster reactivation with another localization. Shortly before the onset of the acute retinal necrosis syndrome she had had a subtle involvement of the ipsilateral trigeminal nerve.

The frequency of a subclinical intracerebral infection with herpes simplex or varicella-zoster virus in the presence of acute retinal necrosis is unknown. If a frequent association is

present, serodiagnostic procedures may have important clinical implications. For direct proof of the viral origin, demonstration of the virus, viral antigen, or viral DNA in infected tissue is required. In cases in which retinal or vitreal biopsies may not be feasible, serologic investigation of the cerebrospinal fluid may be used to corroborate the presumed clinical diagnosis. Since serologic investigations are rapid, antiviral therapy may be contemplated at an earlier stage in such cases, and corticosteroid therapy without antiviral treatment may be avoided. Most cases of acute retinal necrosis, such as ours, seem to represent reactivation of a latent infection with either herpes simplex or varicella-zoster virus. In many cases the fellow eye becomes involved even after as many as 11 years.<sup>30</sup> Since a common cold has often been reported to precede exacerbations of acute retinal necrosis,<sup>22-25,30-32</sup> as in our second case, repeated short-term antiviral therapy may be considered.

The acute retinal necrosis syndrome is a syndrome in the true sense, since not only both eyes but also the central nervous system may be involved. Access to carefully selected serologic tools, as well as advanced neuroimaging, will enable further elucidation of the origin and the extent of intracerebral involvement in the acute retinal necrosis syndrome. Recently developed techniques for analyses of DNA of herpesvirus<sup>15</sup> and varicella-zoster virus by polymerase chain reaction will also be used to obtain direct proof of intraocular infection implicated by the serodiagnosis of the cerebrospinal fluid.

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# Full-Field Electroretinograms in Patients With the Carbohydrate-Deficient Glycoprotein Syndrome

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and Kerstin Strömberg, Ph.D.

We examined five patients who had carbohydrate-deficient glycoprotein syndrome with full-field electroretinograms. Only two of the patients showed fundus changes typical for retinitis pigmentosa, whereas abnormal electroretinograms were seen in all patients. There was no recordable rod response; however, a delay in the cone b-wave implicit time was noted. All patients had nyctalopia. These observations suggest that patients with the carbohydrate-deficient glycoprotein syndrome have a progressive tapetoretinal degenerative disorder of the retinitis pigmentosa type with defined alterations in the electroretinogram.

**R**ECENTLY A NEW DISORDER, the carbohydrate-deficient glycoprotein syndrome, has been described.<sup>1,2</sup> This multisystem disorder exhibits symptoms mainly of the nervous system and also of the liver, kidneys, subcutaneous adipose tissue, skeletal system, and pericardium. The clinical course is different according to age periods.<sup>3,4</sup> The dominating symptoms during infancy and early childhood are failure to thrive, transient liver dysfunction, marked developmental delay, hypotonia with muscular weakness, and occasionally life-threatening hy-

poreflexia. Episodes resembling stroke or pericardial effusions occur. In later childhood, mental retardation, ataxia, slowly progressive polyneuropathy, and secondary skeletal deformities are characteristic findings. In puberty and adulthood, the clinical course is stationary with only minor progressing symptoms (with muscular weakness in the legs, contractures, a compressed stature, and hypogonadism).

Ocular involvement has been observed in ten children with this syndrome.<sup>5</sup> All had esotropia with bilateral abduction deficiency and nystagmoid movements with attempted abduction. All patients whose visual acuity could be tested had poor vision. Retinitis pigmentosa verified by electroretinograms was found to be associated with the condition in some of the patients.<sup>5</sup> Carbohydrate-deficient serum transferrin in the form of disialic and asialic transferrin instead of the normal tetrasialic form serves as a chemical marker for the disease. The chemical marker can be disclosed by isoelectric focusing or by quantitative analysis by rapid microanion exchange chromatography assay.<sup>6,7</sup>

Full-field electroretinograms can be used for detecting and classifying retinal degenerations in early stages.<sup>8</sup> By the use of a narrow-band filter and computer averaging technique it is possible to extend the lower limit of detectability to 0.05  $\mu$ V. We used this method to examine five patients with the carbohydrate-deficient glycoprotein syndrome who ranged in age from 8 to 46 years.

## Patients and Methods

Five patients (one girl, three boys, and one woman), aged 8, 10, 14, 15, and 48, respectively, were examined. All had the characteristic clinical features of the carbohydrate-deficient glycoprotein syndrome. The four youngest patients (Cases 1 through 4) had had failure to

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thrive in infancy, delayed psychomotor development, ataxia, and polyneuropathy. Three patients (Cases 1 through 3) had had several transient episodes resembling strokes, and one (Case 3) had pericarditis, which necessitated pericardiectomy. The older woman (Case 5) was mentally retarded, hypogonadic, and had a severely compressed stature. Computed tomographic brain scans in four of the patients showed cerebellar atrophy. The diagnosis of carbohydrate-deficient glycoprotein syndrome was in all cases confirmed by the finding of greatly increased values of carbohydrate-deficient serum transferrin.<sup>5</sup> The patients are described in a comprehensive pediatric review.<sup>3,4</sup>

The ophthalmic examination of all patients included slit-lamp biomicroscopy, ophthalmoscopy with dilated pupils, and ocular motility testing. Because of young age or mental retardation, visual acuities and visual fields could not be accurately examined. For the same reason, we do not have good fundus photographs available. The parents of the children were informed about the objectives of the examination.

Full-field electroretinograms were obtained in all patients. In each, the pupils were dilated with topical 10% phenylephrine and 1% cyclopentolate hydrochloride. For recording the responses, a Burian-Allen bipolar contact lens electrode was used together with a ground electrode on the forehead. Each patient was dark adapted for 45 minutes before the electroretinographic testing, except one child (Case 4) who was tested under general anesthesia. In this patient, one eye was occluded before the preanesthetic sedation (more than 30 minutes before the start of the measurements), and the fellow eye was patched when the child was asleep. The measurements were started on the first eye and continued on the fellow eye after it had been patched for about 30 minutes.

A Nicolet Compact Four analysis system (Nicolet Biomedical Instruments, Madison, Wisconsin) was used as previously described, using full-field flashes with blue, red, white, or 30-Hz flickering white light.<sup>9</sup> For the detection of small signals, an analogue external narrow bandpass filter was added to the Nicolet Compact Four machine (Kron-Hite, Narrow Band Tracking Filter, model 3800). This filter was tuned to 30 Hz (-12 dB at 29 Hz and 31 Hz) when responses to flickering light (30 Hz; average of 200 light flashes) were obtained. Cone b-wave amplitudes of 1  $\mu$ V or less could only be reliably measured by using computer averaging

and the analog narrow-band filter. By using this system it was possible when stimulating with 30-Hz flickering light to extend the lower limit of detectability to 0.05  $\mu$ V, which is about 0.02% of the peak response in normal subjects.<sup>10</sup> The normal range for the white light is 0.5 Hz, and 30-Hz responses were determined in 83 patients referred to the Department of Ophthalmology in Lund for various reasons, but with no detectable disorder.

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## Results

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Results of the slit-lamp examination were normal in four of the patients, but in the oldest (Case 5), a central posterior cataract was found in both eyes. Esotropia of varying degrees was found in all five patients. In only two of the patients (Cases 4 and 5), careful ophthalmoscopic examinations disclosed retinal changes, comprising spicular pigment deposits and narrow vessels in all four quadrants. The retinal pigmentation, the vessels, the shape, color, and size of the optic disk, and the peripheral retina were otherwise in the normal range in the other three patients (Cases 1, 2, and 3). On interrogation, the caretakers stated that the patients had night vision problems.

Full-field electroretinograms with blue and red light flashes showed no rod responses in any of the patients, but a small cone response to red light flashes could be detected in the youngest (Case 1). After dark adaptation, white light flashes elicited measurable b-wave responses in four of the patients (Cases 1 through 4). When stimulating with full-field 30-Hz flickering white light and using the narrow-band filter, residual cone b-wave responses could be measured in all patients. The cone implicit time for 30-Hz flickering white light was delayed for all patients (Table). The normal control subjects had a higher median age (26 years), but this was not expected to influence the electroretinographic responses (Figure).<sup>11</sup>

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## Discussion

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All five patients with the carbohydrate-deficient glycoprotein syndrome had pathologic electroretinograms with a reduction in the amplitude of the response to standard 0.5-Hz white light of more than 50% (Table). These

**TABLE**  
ELECTRORETINOGRAM MEASUREMENTS IN FIVE  
PATIENTS WITH THE CARBOHYDRATE-DEFICIENT  
GLYCOPROTEIN SYNDROME\*

	WHITE LIGHT AMPLITUDE ( $\mu$ V)	30-HZ FLICKERING AMPLITUDE ( $\mu$ V)	WHITE LIGHT IMPLICIT TIME (MSEC)
Cases 1-4 (median age, 12 years) (S.E.M.)	39.9 $\pm 11.5$	23.10 $\pm 8.50$	38.60 $\pm 1.37$
Case 5 (48 years)	ND	0.14	35.60
Normal subjects (N = 83) (S.E.M.)	303.0 $\pm 10.6$	59.50 $\pm 2.13$	29.40 $\pm 0.18$

\*S.E.M. indicates standard error of the mean, and ND indicates not detectable.

findings indicate a widespread photoreceptor loss.

No rod responses could be detected in the electroretinograms in any of the patients with the carbohydrate-deficient glycoprotein syndrome, which is a characteristic finding in patients with tapetoretinal disorders with nyctalopia.<sup>8</sup> This suggests that patients with carbohydrate-deficient glycoprotein syndrome have night vision problems, which was corroborated by the observations of the patients' caretakers. In these patients nyctalopia is often impossible to assess more accurately with dark adaptation tests in the conventional examination.

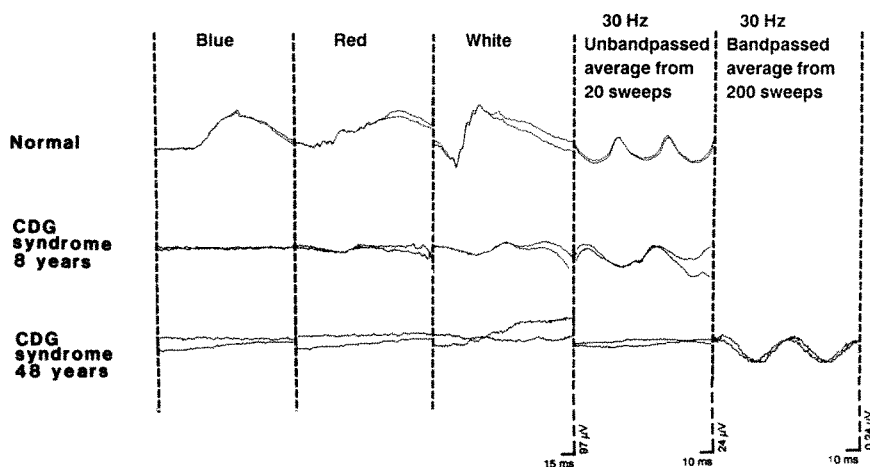
In contrast to the absent rod responses, the

cone responses were in the lower normal range in the young patients. The cone b-wave implicit time, however, was delayed in all patients (Table). Such an observation is considered indicative of a progressive retinal disease.<sup>12</sup> We therefore presume that the retinal disorder in patients with carbohydrate-deficient glycoprotein syndrome is progressive.

It can be difficult to assess the visual capacity in these mentally retarded patients. The ophthalmoscopic examination in three of them (Case 1, 2, and 3) showed no changes suggesting retinitis pigmentosa, and some of the patients had been repeatedly examined before the carbohydrate-deficient glycoprotein syndrome was identified without any retinal disease being diagnosed. In patients like these, full-field electroretinogram analysis is of obvious help when assessing visual problems.

All previously described patients with the carbohydrate-deficient glycoprotein syndrome have been young, the oldest being 21 years.<sup>2</sup> We included one older patient, age 48 years, with remaining useful vision and some residual cone function as shown by the electroretinogram. Although the electrophysiologic investigations suggest that patients with carbohydrate-deficient glycoprotein syndrome have a retinitis pigmentosa-type tapetoretinal disorder, the preserved vision in the 48-year-old patient and her relatively well-preserved electroretinogram suggest that the disease does not invariably result in blindness.

All our patients with the carbohydrate-deficient glycoprotein syndrome had some degree of visual impairment and a pathologic electroretinogram (no rod response and a prolonged cone b-wave implicit time), which suggest that



**Figure** (Andréasson and associates). Full-field electroretinograms from a normal subject and two patients (Cases 1 and 5) with carbohydrate-deficient glycoprotein syndrome (CDG).



patients with the syndrome have a progressive tapetoretinal degenerative disorder of the retinitis pigmentosa type with nyctalopia. The two major proteins associated with the photoreceptors, opsin and interphotoreceptor retinoid-binding protein, both are glycosylated, and the carbohydrate-deficient glycoprotein syndrome is indeed a defect in the glycosylation of proteins. Patients with retinitis pigmentosa are known to have a reduction in the opsin and interphotoreceptor retinoid-binding protein in the retina, but this has been attributed to the photoreceptor loss.<sup>13</sup> Glycosylation inhibition is known to affect the disk regeneration in frog photoreceptors,<sup>14</sup> but it remains undetermined to what extent and by which mechanism glycosylation defects can induce a tapetoretinal degeneration.

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### OPHTHALMIC MINIATURE

In brief, I believe that I may hold the expectation not to be exaggerated, that all the alterations of the vitreous body and of the retina which, until now, have been found in cadavers, will also permit of recognition in the living eye—a possibility which appears to promise the most remarkable advances for the hitherto undeveloped pathology of this structure.

Von Helmholtz, H.; Shastid, T. H. (trans.) *The Description of an Ophthalmoscope* (1851)

Chicago, Cleveland Press, 1916, p. 29

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## PERSPECTIVES

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### The Laser Step in Early Glaucoma Therapy

E. Michael Van Buskirk, M.D.

The Glaucoma Laser Trial has raised questions about the appropriate place of argon laser trabeculoplasty in the treatment of open-angle glaucoma.<sup>1</sup> The Glaucoma Laser Trial Research Group concluded that the study encouraged the application of laser trabeculoplasty as initial therapy by postponing the onset of medical therapy with its attendant inconvenience and risk of drug side effects.<sup>1</sup> In an accompanying editorial, however, Lichter<sup>2</sup> urged caution about overinterpreting the data. At the same time, ophthalmologists receive communications from laser manufacturers urging initial treatment. A professional tabloid reports that every patient with glaucoma has a "right" to early laser treatment and touts that "Initial Laser Tops Drugs for Control."<sup>3</sup> Thus, we must legitimately question where laser treatment fits in the scheme of lifelong glaucoma therapy. Indeed, with the recent studies of initial surgi-

cal therapy, the entire spectrum of sequential glaucoma therapy has come under renewed scrutiny.<sup>4</sup>

The concept of laser trabeculoplasty has been confusing from its inception. Many interested observers were skeptical about initial reports that nonpenetrating trabecular laser burns could produce a lasting hypotensive response.<sup>5,6</sup> A monkey model of laser-induced ocular hypertension was not terribly different from the hypotensive clinical treatment being proposed.<sup>7</sup> Multiple subsequent studies,<sup>8-12</sup> however, substantiated the lasting hypotensive response to trabecular laser initially reported by Wise and Witter.<sup>6</sup> Subsequently, argon laser trabeculoplasty has assumed a routine role in the treatment of patients with open-angle glaucoma, although its appropriate place in sequential therapy remains controversial.

Studies of the 1980s have demonstrated that



laser trabeculoplasty predictably reduces intraocular pressure in the vast majority of treated subjects. The hypotensive effects appear to be additive to most pharmacologic hypotensive agents. Despite the initially encouraging response, the hypotensive effect progressively diminishes over time, with an annual rate of about 10% of successful treatments failing or the patients requiring additional therapy.<sup>13,14</sup> This failure rate does not impugn laser therapy as a valid treatment. Primary open-angle and similar glaucomas develop from progressive trabecular outflow obstruction, a process that would be expected to proceed with or without laser therapy. Some studies suggested that after initially successful complete 360-degree laser treatment that subsequently failed, repeat laser treatment again significantly reduced intraocular pressure in responsive patients.<sup>15,16</sup> Other studies showed little benefit to repeat treatment.<sup>17,18</sup>

The exact pressure-lowering mechanism of laser trabecular therapy remains unknown, but the same can be said for miotic and adrenergic drug therapy. Despite the catchy name, trabeculoplasty, there is little evidence that there is much plastic effect and some data to the contrary.<sup>12,19-21</sup> Some studies suggested that laser initiated a cascade of biologic events, similar to the response to some drugs.<sup>19,21-27</sup>

Clinically, the hypotensive response appears to be relatively independent of the wavelength or character of laser, the location or extent of the laser burns within the trabeculum, and the specific mechanism of noninflammatory open-angle glaucoma.<sup>11,14,28-35</sup> Thus, from the studies of the 1980s, laser treatment of the trabecular meshwork, like pharmacologic treatment, appears to reduce intraocular pressure nonspecifically for a finite period of time and is renewable with reapplication in some highly responsive patients.

In the mid 1980s, The Glaucoma Laser Trial research group sought to compare the effects of laser trabecular treatment to medical treatment in patients with newly diagnosed glaucoma.<sup>36</sup> Based upon studies to date, many published after the Glaucoma Laser Trial, one would predict a nonspecific, substantial, but temporary, decrease in intraocular pressure in eyes receiving laser therapy, essentially the result of the trial.

Comparison of the relative efficacy of laser to medical therapy becomes more difficult, particularly in determining the appropriate place of each modality in the sequence of therapy. Eco-

omic factors now loom increasingly important in decisions about the appropriateness of a given therapy. Whether delaying the onset of medical therapy for two years produces any real advantage for the quality of life, blindness prevention, or the economics of glaucoma care can be debated for society as a whole and for an individual patient facing a lifelong need for some sort of therapy. The cost of a single laser treatment compares favorably to two years of a single drug therapy with a beta blocker.

Some real concerns arise, however, about interpreting the Glaucoma Laser Trial data.<sup>1</sup> A sequence of steps of medical therapy were defined, starting with timolol, progressing to dipivefrin, low-dose pilocarpine, high-dose pilocarpine, and then combined therapy.<sup>1</sup> On the day of treatment, one eye received laser therapy and the fellow eye received timolol. When therapy was advanced, the next prescribed step in the sequence of therapy was used. Because the laser-treated eye received timolol as Step 2, however, the various steps in advancing medical therapy were never comparable between the two eyes<sup>1</sup> (Table).

The data showed that, of the laser-treated eyes, just over half required additional medical therapy within two years. In other words, a patient receiving laser therapy faces a greater than 50% chance of requiring medicines within

**TABLE**  
THERAPEUTIC STEPS IN THE GLAUCOMA LASER TRIAL<sup>1</sup>

STEP NO.	LASER FIRST	MEDICINE FIRST
1	Argon laser trabeculoplasty	Timolol
2	Argon laser trabeculoplasty plus timolol	Dipivefrin
3	Argon laser trabeculoplasty plus dipivefrin	Low-dose pilocarpine
4	Argon laser trabeculoplasty plus low-dose pilocarpine	High-dose pilocarpine
5	Argon laser trabeculoplasty plus high-dose pilocarpine	Timolol plus high-dose pilocarpine
6	Argon laser trabeculoplasty plus timolol plus high-dose pilocarpine	Dipivefrin plus high-dose pilocarpine

two years.<sup>1</sup> Furthermore, the study showed that the timolol-treated eyes that required additional therapy underwent twice as many steps or changes in medications as did the laser-treated eyes, but the advancing steps of therapy were different between the laser- and drug-treated eyes<sup>1</sup> (Table). Ominous was the suggestion that visual field deterioration accounted for nearly twice as many medication step changes in the laser-treated as the nonlaser-treated eyes.<sup>1,2</sup> Thus, a factor in favor of initial laser treatment is the two-year delay in drug treatment. Two years' grace from drug therapy is relatively meaningless at the onset of an adult life of glaucoma therapy, although it may be worthwhile for elderly patients hoping to retain vision without surgery during their waning years.

Eyes treated initially with laser therapy required only half as many step changes in subsequent medical therapy as did those eyes treated initially with timolol. At first blush, this seems the greatest advantage of laser therapy, but this conclusion requires more serious examination of the study design and results. The laser-treated eyes received laser treatment as Step 1 with the addition of timolol as Step 2. The nonlaser-treated eyes received timolol as Step 1 with the withdrawal of timolol and the substitution of dipivefrin as Step 2.<sup>1</sup> Thus, in Step 2, the laser-treated eyes had already had laser therapy and were receiving timolol, but the medically treated eyes were receiving dipivefrin alone<sup>1</sup> (Table). In essence, for the laser-treated eyes, Step 2 became a giant step ahead, but, for the nonlaser-treated eyes, Step 2 was a leap backward! It should come as no surprise that the medically treated eyes required a move beyond Step 2 to Step 3 or 4, since they had to go all the way to Step 5 before again becoming eligible to receive a significant aqueous humor suppressant (Table). Thus, the previous stipulation in the study design for dipivefrin as Step 2 for the timolol-treated eyes and timolol as Step 2 for the laser-treated eyes invalidates using the number of therapy step changes as an index of relative therapeutic efficacy.

The Glaucoma Laser Trial has shown conclusively that initial laser treatment offers no real advantage to medical therapy for the patient with newly diagnosed glaucoma, except a couple of years' grace before starting other medications. The economics are similar. The risk of advancing neuropathy is similar. The relative requirement for additional medications cannot be answered because of flaws in the study

design. In some respects, the study suggests initial laser treatment to be disadvantageous compared to laser treatment placed toward the end of the medical sequence of therapy. More than half of the eyes treated initially with laser therapy required advancement in therapy after only two years. In other studies of eyes that received laser therapy after maximal medical therapy, about five years passed before 50% failed.<sup>13,14</sup> Unless the laser effect is renewable, the modality may be wasted in the early years of treatment, which denies its later benefit when medical alternatives have been exhausted and the patient faces surgery.

Because of the incomparability of the sequential medication steps, the Glaucoma Laser Trial was no giant step for mankind. At best, it shows initial laser therapy to be of little if any value compared to conventional medical treatment. At worst, misinterpretation opens the door for commercial and professional exploitation of a highly remunerative procedure.

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## LETTERS TO THE JOURNAL

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### Central Retinal Artery Occlusion in a Child After General Anesthesia

**Anthony Locastro, M.D.,  
Kenneth D. Novak, M.D.,  
and Albert W. Biglan, M.D.**

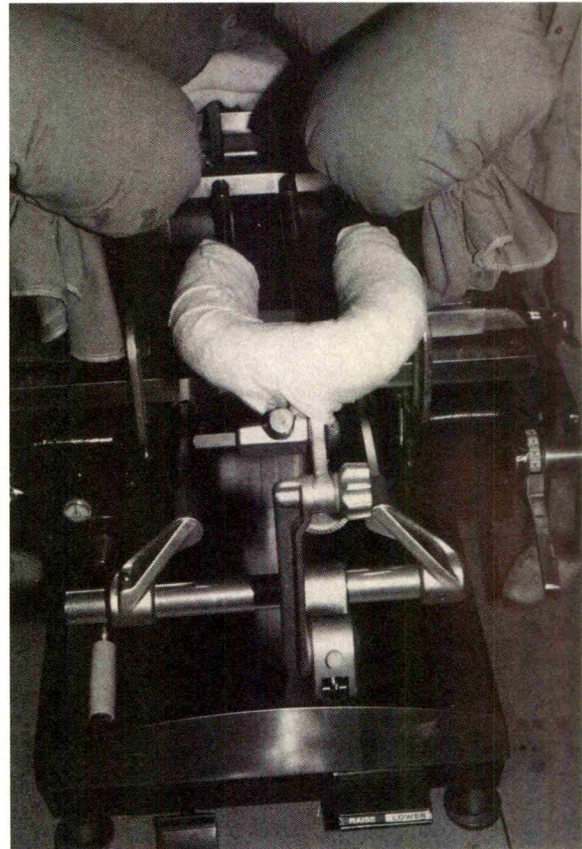
Department of Ophthalmology, University of Pittsburgh School of Medicine. This study was supported in part by grants to the Children's Eye Clinic, Children's Hospital of Pittsburgh from Fight for Sight, Inc.

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Occlusion of the central retinal artery is uncommon in children. Brown, Magaral, and Shields<sup>1</sup> studied 27 children and young adults who developed retinal artery obstruction and found an association with migraine, coagulation abnormalities, trauma, sickle cell disease, cardiac disorders, use of oral contraceptives, pregnancy, drusen of the optic disk, and increased intraocular pressure. None of the cases occurred under general anesthesia. We treated a healthy 12-year-old girl who developed a central retinal artery occlusion during a procedure to correct scoliosis of the spine.

A 12-year-old girl underwent posterior spinal fusion of the third thoracic and first lumbar vertebrae with an iliac crest graft and rib excision. During this eight-hour operation, the patient was in a prone position with her face resting on a padded head ring (Fig. 1). Throughout the procedure, there was no hypotension (blood pressure less than 100/60 mm Hg), and the blood volume was maintained. Continuous monitoring showed blood oxygen saturation to be completely maintained.

In the recovery area, ecchymosis and edema of the right eyelids were observed, and the iris was noted to be discolored. An ophthalmology consultation confirmed the eyelid ecchymosis



**Fig. 1** (Locastro, Novak, and Biglan). The padded headrest that was used to protect the eyes during the operation.

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and edema. The iris was discolored because of layering of a hyphema, and the right pupil showed an afferent defect. Intraocular pressure was normal. The fundus of the right eye showed the retinal vessels perfusing the retina, and there was intraretinal edema that involved the posterior pole, excluding the macula. The left eye was normal. No evidence of emboli, hemorrhage, or optic disk drusen was found. Because the retina was being perfused, it was elected not to institute treatment.

Results of cardiac evaluation with echocardiogram, hemoglobin electrophoresis, and coagulation studies were unremarkable. The patient did not have migraine, and she did not use oral contraceptives.

Twenty hours later the patient had visual acuity of R.E.: no light perception and L.E.: 20/20. The afferent pupillary defect and retinal edema persisted. Three months later, visual acuity remained no light perception in the right eye. The retinal edema had resolved, and there was atrophy of the optic nerve (Fig. 2).

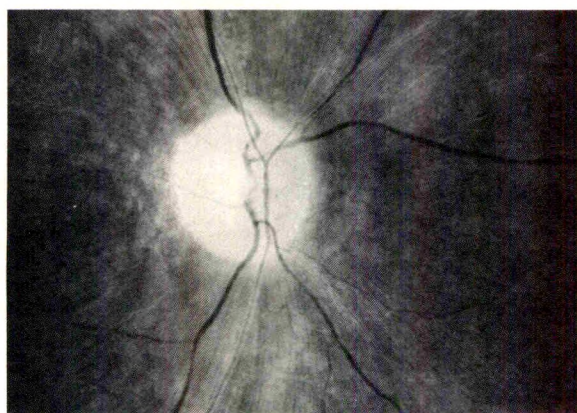
Reports of blindness after general anesthesia is uncommon,<sup>2</sup> especially in children. Hollenhorst, Svein, and Benoit<sup>3</sup> described eight patients, ranging in age from 29 to 50 years, who lost vision after having undergone a neurosurgical procedure requiring a posterior approach. As in our case, the patients' faces were cushioned in well-padded headrests. Two of the patients had hypotensive episodes. At the conclusion of the procedure, visual acuity of hand motions in the affected eye and retinal edema with afferent pupillary defects were consistent findings in these two patients. Final visual acuity ranged from 20/15 to no light percep-

tion, with visual acuity of hand motions or worse in five patients. In an effort to elucidate the cause of the artery occlusion, Hollenhorst, Svein, and Benoit<sup>3</sup> performed studies on primates. They concluded that the common denominator when vision was lost was application of pressure to the eyeball. They were unable to conclude that shock was a prerequisite for this condition.

Because of the frequency of spinal fusion in children and the need for early recognition and treatment to prevent loss of vision, we encourage careful monitoring of the face, protection of the eye and orbits during these operations, and prompt consultation if injury is suspected.

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**Fig. 2** (Lacastro, Novak, and Biglan). The optic nerve of the right eye shows early signs of atrophy three weeks after the operation.

## Management of Exudative Retinal Detachment After Plaque Therapy for Intraocular Melanoma

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Progressive massive exudative retinal detachment that occurs as a complication of ocular episcleral plaque radiotherapy for choroidal or ciliary body melanoma<sup>1,2</sup> commonly leads to total loss of vision in the affected eye and occasionally prompts the surgeon to recommend enucleation.<sup>3</sup> Based on previous experi-

ence with this phenomenon, we treated a patient with delayed exudative retinal detachment after plaque radiotherapy by vitrectomy, internal drainage of subretinal fluid, and endolaser in an attempt to reattach the retina and preserve vision.

A 49-year-old woman had flashing lights in the left eye of two weeks' duration. Ophthalmic examination disclosed a brown cilio-choroidal mass measuring  $11 \times 9$  mm in basal diameters by 4.5 mm in thickness nasally in the left eye. Standardized A-scan ultrasonography disclosed low-amplitude internal reflectivity consistent with malignant melanoma. The tumor was associated with a nonrhegmatogenous retinal detachment with clear shifting subretinal fluid involving 50% of the retina.

The patient was treated by episcleral ruthenium 106 plaque radiotherapy using a 15-mm diameter ophthalmic applicator. The total implantation time was 119.7 hours. The dose was 41,871 cGy at 1 mm and 9,313 cGy at the tumor apex.

The patient did well postoperatively and showed satisfactory local tumor regression and resolution of all subretinal fluid. Approximately four months after treatment, however, she began to develop an exudative detachment inferiorly. The detachment increased progressively in extent and threatened the macula. Visual acuity was still correctable to 20/20. An attempt was made to drain the subretinal fluid and reattach the retina. This was accomplished by pars plana vitrectomy with internal drainage of subretinal fluid and fluid-air exchange followed by scatter endophotocoagulation to the previously detached inferior retina. Cytologic assessment of the subretinal fluid disclosed no malignant cells.

Three months postoperatively visual acuity decreased to 20/400 because of reaccumulation of subretinal fluid extending to the macula. This redetachment was managed in the office by repeat fluid-air exchange. The subretinal fluid gradually resolved over one month. Four months after her vitrectomy, she was given additional scatter laser treatment over the inferior one half of the retina and tumor. The retina has remained flat with no further reaccumulation of subretinal fluid. The patient has subsequently undergone uncomplicated extracapsular cataract extraction with implantation of a posterior chamber intraocular lens. She has done well postoperatively, maintaining stable postirradiation tumor regression and complete retinal attachment. At the most recent follow-

up examination 37 months after plaque therapy, visual acuity was correctable to 20/50.

Progressive exudative retinal detachment after episcleral plaque radiotherapy for a posterior uveal melanoma is uncommon.<sup>1,2</sup> Detachments of this type, however, tend to be relentlessly progressive in many affected patients once they become bullous. Such detachments are commonly complicated by rapid total opacification of the lens, phacomorphic angle-closure or neovascular glaucoma, complete loss of vision in the eye, and severe pain. Because of these complications, most patients who develop this problem have undergone enucleation.<sup>3</sup> Patients who have tolerated their total bullous exudative retinal detachment after plaque therapy and have not undergone enucleation eventually have spontaneous retinal reattachment; unfortunately, however, the retina in such cases is severely disorganized, and the vision does not return.

In our patient, we intervened surgically just when the exudative retinal detachment was starting to become bullous. We believe that we have prevented total loss of vision and other possible postirradiation ocular complications. We cannot conclude, of course, from this single case that the intervention we used was truly appropriate or that it was convincingly better than what we would have observed without treatment. We recognize the concerns of many of our colleagues that intraocular surgery (let alone any additional ocular manipulation) on an eye containing a posterior uveal melanoma may increase the patient's risk of death from metastatic melanoma. Conversely, we are unaware of any compelling clinical data in support of this concern. We believe that we have preserved our patient's eye with useful vision, and we are optimistic that our postirradiation ocular surgery has not compromised our patient's chances for long-term melanoma-free survival.

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## Severe Anaphylactic Reaction to Orally Administered Fluorescein

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A 65-year-old woman with an eight-year history of type II diabetes had been uneventfully examined with the use of fluorescein angiography three times during the preceding 12 months, with intravenous administration on the first two occasions and oral administration on the third. On the second oral fluorescein angiography examination (four months after the first), she was given four 500-mg fluorescein capsules. One hour later she began to have difficulty in breathing, incontinence, bradycardia, and arterial hypotension (65/40 mm Hg) and had a swollen neck and glottal edema with a blood glucose level of 120 mg. After immediate intravenous administration of 40 mg of prednisolone, her breathing was eased, and arterial pressure increased to 100/70 mm Hg. A few hours later she recovered; there was no recurrence of the symptoms during the next six hours of observation or during the following 48 hours.

The patient had no medical or family history of atopy. We have used oral fluorescein angiography on 109 occasions previously with no abnormal reactions, including those with the same capsules. The patient had been given fluorescein three times in the previous year (twice intravenously and once orally), which suggests that she had been sensitized to sodium fluorescein or the excipient.

The dose of fluorescein administered (one 500-mg capsule per 15 kg of body weight) was also used by Quentel, Attali, and Coscas.<sup>1</sup> Kinsella and Mooney<sup>2</sup> described anaphylaxis in

a 16-year-old boy 20 minutes after administration of 5 ml of a 25% solution of sodium fluorescein in orange juice (1.25 g/100 ml).

Anaphylactic reaction rates for intravenous fluorescein angiography have been reported to be below 0.6%.<sup>3,4</sup> Our case constitutes 0.9% of the 110 examinations we have performed with the oral technique. One of the advantages of this technique is the absence of serious adverse reactions.<sup>5</sup> Although these two reported cases of anaphylaxis do not rule out the use of oral fluorescein angiography, the findings do imply that patients should be warned of the possibility of reaction and that they should be observed for a few hours after administration.

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## Hepatic Cirrhosis as a Cause of Eyelid Retraction

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Although Bartley and Gorman<sup>1</sup> believe that hepatic cirrhosis does not cause eyelid retraction, I have treated a patient in whom there seems to be little doubt that true eyelid retraction was caused by hepatic cirrhosis. Photo-

graphs of this patient have been published elsewhere.<sup>2</sup>

In October 1971, a 41-year-old man was admitted to the Johns Hopkins Hospital because of jaundice, ascites, and a personality change associated with chronic alcohol abuse. Physical examination disclosed an increased hemidiaphragm with poor excursion, massive ascites, a prominent superficial venous pattern across the abdomen with other evidence of portal hypertension, including an enlarged liver and spleen, scrotal edema, presacral edema, and peripheral edema. Esophagoscopy disclosed numerous varices. The patient was tremulous and had a blunted affect, but he had no asterixis. Additionally, he had marked eyelid retraction, without proptosis or orbital congestion. The patient had no history of thyroid dysfunction. Results of tests of thyroid function, including measurements of serum thyroxin and triiodothyronine in the serum, and a Werner suppression test were normal. While at the hospital, the patient had a massive gastrointestinal hemorrhage from a duodenal ulcer; however, he gradually recovered and was eventually discharged from the hospital approximately six weeks after admission. He was followed up by a gastroenterologist for the next two years, during which time his liver function became normal and his eyelid retraction resolved. He subsequently moved to Florida where he was followed up at regular intervals by both a gastroenterologist and an ophthalmologist for the next ten years. He died of cancer in 1990. He had never developed any clinical or laboratory evidence of thyroid disease and had never had any recurrence of his eyelid retraction.

It would appear that this patient had Summerskill's sign, eyelid retraction from hepatic cirrhosis, and that the condition resolved with the successful treatment of the cirrhosis.

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### Response of Reactivated Ligneous Conjunctivitis to Topical Cyclosporine

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Ligneous conjunctivitis is a rare disorder, which is characterized by an aberrant response to inflammation. The condition often begins in early childhood and may involve the upper and lower tarsal as well as the bulbar conjunctiva.<sup>1</sup> The precipitating factor may be a local injury or a part of a multisystem response to a systemic process.<sup>2</sup> These injuries include bacterial, viral, and fungal infections, toxins, allergy, and trauma. Spontaneous resolution has been reported, but the clinical course often lasts many years with frequent recurrences.<sup>1</sup> Surgical removal alone usually results in regrowth of the membrane in as few as two days. More recently, excisional biopsy and topical cyclosporine have been advocated.<sup>3</sup>

An 11-year-old girl had an upper respiratory infection and concurrent conjunctivitis.<sup>3</sup> Nine years later, after recurrent bouts of her disease, she was referred to the National Institutes of Health where she underwent surgical stripping of the membrane and treatment with topical cyclosporine (2% solution) and topical corticosteroids. Immunohistochemical studies of the excised tissue showed a 3:1 ratio of CD4+/CD8+ with 75% of the T lymphocytes expressing an interleukin-2 receptor, focal accumulation of plasma cells, and B lymphocytes.<sup>3</sup> Immunofluorescence showed IgG as a prominent component of the amorphous hyaline material. Fibrin and fibrinogen were also present. After several months the lesions regressed. The condition remained in remission, and the patient was asymptomatic without evidence of any lesions after cessation of all topical eyedrops.

Four years after stopping cyclosporine, the patient again developed active lesions. Oral



penicillin had been started one week earlier for culture-positive *B streptococcus* pharyngitis. Conjunctival Gram stain showed no organisms and few granulocytes and monocytes. A regimen of gentamicin sulfate, prednisolone acetate, and cyclosporine eyedrops was begun. Conjunctival cultures grew *Haemophilus influenzae* and scant *Staphylococcus aureus*. After several months with continued topically administered cyclosporine, the lesions regressed to atrophic scars. The cyclosporine was tapered during a four-month period. The condition has remained in remission, and the patient continues to be asymptomatic without evidence of any active lesions after cessation of all topical eyedrops.

Cyclosporine affects the ability of the T lymphocytes to produce and use lymphokine interleukin-2. Because of the lipid solubility of cyclosporine, high levels can be measured in conjunctiva, sclera, and corneal epithelium. In a randomized study, topically administered cyclosporine was demonstrated to be effective in treating vernal keratoconjunctivitis.<sup>4</sup>

Trauma, hypersensitivity, and infection have all been proposed as contributors to this condition. The injury resulting in the reactivation of this patient's disease, which had been in complete remission for four years, was likely her localized upper respiratory infection and concomitant bacterial conjunctivitis. Before initiating treatment with topical cyclosporine four years previously, she had a ten-year history of recurring lesions, without substantial control of symptoms. She had been treated with topical corticosteroids, sodium cromolyn 4%, hyaluronidase, and thiotepa without success. Topical cyclosporine in conjunction with topical corticosteroids suppressed episodes of reactivation of ligneous conjunctivitis and relieved the discomfort.

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## Bilateral Follicular Conjunctivitis as a Manifestation of Lyme Disease

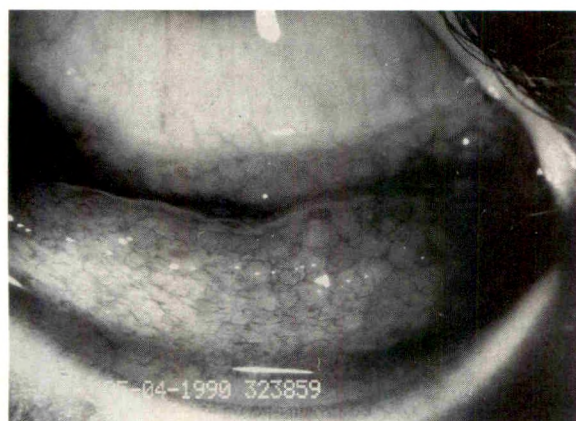
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Lyme borreliosis is a spirochetosis, which is caused by *Borrelia burgdorferi* and transmitted by the Ixodidae ticks. In the different stages of the disease, dermatologic, neurologic, cardiac, and joint abnormalities can occur.<sup>1,2</sup> The most common ocular manifestation of Lyme disease is a transient mild conjunctivitis in the early stage,<sup>3,4</sup> but isolated cases of interstitial keratitis, episcleritis, iridocyclitis, vitreitis, panophthalmitis, optic disk edema, diffuse choroiditis with exudative retinal detachment, ischemic optic neuropathy, optic neuritis, neuroretinitis, orbital myositis, paresis of the oculomotor or abducent nerve, and pseudotumor cerebri have been reported.<sup>2,5</sup> We treated a patient with Lyme disease in whom the only signs of the disease were eyelid swelling, bilateral follicular conjunctivitis, and unilateral regional lymphadenopathy.

In August 1989, a 12-year-old boy was bitten by a tick on the left lower eyelid during a vacation at a camp in the region of Antwerp, Belgium. The tick was detected and removed manually the next day by his father. A family physician, who was consulted because of the left eyelid swelling and epiphora, prescribed an oral antihistaminic and sodium cromoglycate eyedrops. Since this treatment during several months failed to improve the ocular condition, the patient was referred to us in March 1990. He had had no malaise, fatigue, or any other general systemic symptom. Neither the patient nor his parents had observed erythema at the site of the bite or in the surrounding area. The



**Figure** (Mombaerts, Maudgal, and Knockaert). Large follicles were noted on the tarsal conjunctiva and in the fornix of the left eye.

left eyelids were more swollen than the right. Large follicles were present on the tarsal conjunctiva and in the fornices of both eyes, but they were more pronounced in the left eye (Figure). The bulbar conjunctiva was hyperemic. The cornea, anterior chamber, vitreous, and fundus of both eyes were normal. Best-corrected visual acuity was 20/20 in each eye. General physical examination disclosed nontender palpable left preauricular and submandibular lymph nodes. There were no other abnormal findings. Cultures of the conjunctival swabs did not grow any bacteria or viruses. Results of serologic tests for *B. burgdorferi*, however, were positive with an immunofluorescence assay titer of greater than 1:128 and an enzyme-linked immunosorbent assay titer of greater than 1:100. A presumptive diagnosis of Lyme disease was made, and topical 0.4% dexamethasone eyedrops were prescribed, which resulted in a decrease of swelling of the eyelids and the size of the follicles. As soon as the diagnosis was confirmed by the results of serologic tests, a regimen of oral doxycycline, 100 mg/day, was started and continued for four weeks. The patient has had no recurrences of the symptoms.

Lyme disease may manifest a wide array of signs and symptoms. Our patient, however, did not recall having erythema chronicum migrans or any period of abnormal fatigue, fever, headache, stiff neck, myalgia, or arthralgia. The only signs and symptoms in this patient were the bilateral eyelid swelling, follicular conjunctivitis, epiphora, and enlarged nontender regional lymph nodes on the side of the tick bite. The

diagnosis of Lyme disease in this case was supported by the history of tick bite, the positive results of the serologic tests (indirect immunofluorescence assay as well as the more specific ELISA), and the response of the disease to specific antibiotic therapy. Although we did not attempt to isolate the causative agent from the involved tissues, the efficacy of the antibiotic therapy suggests the presence of spirochetes, probably at the site of the bite. The partial response to topical corticosteroid treatment may suggest an immune-mediated conjunctivitis. The findings in our patient demonstrate that bilateral follicular conjunctivitis, eyelid swelling, and regional lymphadenopathy may be the only manifestations of Lyme disease if the tick bite is located in the periorbital region.

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## Horner's Syndrome as a Complication of Pacemaker Insertion

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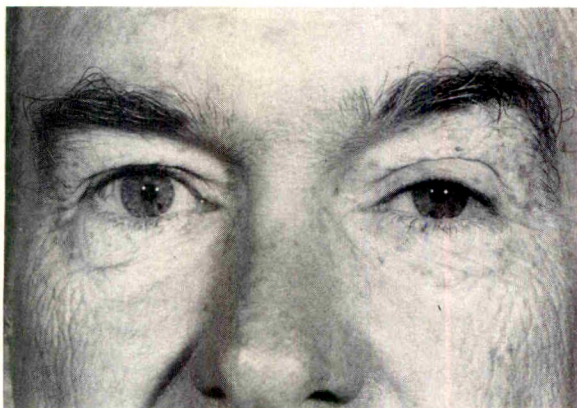
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Horner's syndrome has been reported after numerous surgical procedures involving the thoracic inlet and neck, including intercostal chest drains, internal jugular vein catheterization, interscalene brachial plexus block, carotid angiography, and cardiothoracic surgery.<sup>1</sup> To the list of iatrogenic causes of oculosympathetic paresis, we add a case of a patient who developed Horner's syndrome after percutaneous subclavian vein cannulation for placement of a transvenous cardiac pacemaker.

A 55-year-old man noted the abrupt onset of left-sided blepharoptosis immediately after surgical insertion of a pacemaker. The patient had a history of sick sinus syndrome and had undergone cannulation of the left subclavian vein under local anesthesia. The pacemaker lead was then passed transvenously and embedded in the right ventricle. No intraoperative complications were reported. No other neurologic sequelae were noted. The patient did not have any ipsilateral impairment of sweating, but he indicated that he had limited his physical activity after insertion of his pacemaker.

Examination one week after pacemaker insertion disclosed moderate blepharoptosis of the left upper eyelid with palpebral fissure heights in primary gaze of R.E.: 11 mm and L.E.: 8 mm (Figure). The pupils had anisocoria in bright light with diameters of R.E.: 4 mm and L.E.: 3.5 mm. Anisocoria was more pronounced in dim light with pupillary diameters of R.E.: 6 mm and L.E.: 4 mm. Pupillary light reflexes, extraocular movements, and confrontation visual fields were normal. Results of slit-lamp biomicroscopy were normal, except for the incidental



**Figure** (Gedde and associates). After percutaneous subclavian vein cannulation with insertion of a transvenous cardiac pacemaker, the patient developed left blepharoptosis and anisocoria.

finding of cornea guttata in both eyes. Results of the retinal examination were normal.

Pharmacologic confirmation and localization of the lesion were performed. Topical cocaine 4% was instilled in the inferior conjunctival fornix of each eye; the right pupil dilated, and the left pupil failed to dilate. One week later the pupils were tested with topical hydroxyamphetamine 1%. Both pupils dilated. Results of computed tomography of the chest were negative for any mass lesions; the pacemaker lead was in good position.

Horner's syndrome may be caused by a lesion anywhere along the three-neuron pathway from the hypothalamus to the orbit. Pharmacologic testing localized this patient's lesion to the second (preganglionic) neuron, which leaves the spinal cord at the ciliospinal center of Budge and Waller to ascend up the cervical sympathetic chain and synapse in the superior cervical ganglion. Second neuron oculosympathetic paresis is caused by lesions or trauma in the high thoracic or low cervical regions. The most frequently identified causes of preganglionic Horner's syndrome are neoplasia and trauma.<sup>2-4</sup>

In our patient, the temporal association of the percutaneous subclavian venous pacemaker insertion and the abrupt onset of blepharoptosis and anisocoria implicate the surgical procedure as the cause. Additionally, radiologic examination of the patient's thorax and upper neck disclosed no anatomic abnormalities, such as tumor.

The sympathetic fibers of the ansa subclavia lie in close proximity to the subclavian artery and vein near the apex of the lung, and we speculate that inadvertent trauma to this region during cannulation of the subclavian vein produced Horner's syndrome in this patient. Recent pacemaker insertion should be considered as a possible cause of preganglionic Horner's syndrome.

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## **Fate of the Fellow Eye After *Propionibacterium acnes* Endophthalmitis**

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Chronic postoperative uveitis after extracapsular cataract surgery has become an increasingly important clinical problem. Classically, inflammation directed against lens proteins, mediated by complement-fixing antibodies against the antigens remaining in the residual cortex, has been implicated in the pathogenesis.<sup>1</sup> Thus, the fellow eye would be expected to be at risk for future involvement after cataract surgery, since the antilens autoantibodies would be present in the blood.

In recent years, inflammation associated with chronic *Propionibacterium acnes* infection has become another common cause of postoperative uveitis. Although this syndrome is caused by a localized indolent endophthalmitis, many of the clinical features resemble those of lens-induced uveitis, especially the chronic corticosteroid-responsive iridocyclitis with granulomatous keratic precipitates.<sup>2</sup> Several investigators have postulated that the bacteria might actually trigger lens-induced uveitis, perhaps by acting as an adjuvant to override the patient's immunologic tolerance to their own lens antigens.<sup>2-4</sup> If this hypothesis is true, then antilens autoimmunity would become an important pathogenic mechanism in this syndrome, and the contralateral eye might be at risk for chronic postoperative inflammation after extracapsular cataract surgery.

We investigated the frequency of chronic postoperative inflammation in the fellow eye after *P. acnes*-associated inflammation in the affected eye. We studied all cases of culture-proven *P. acnes* syndrome managed at our insti-

tution between January 1986 and October 1990. We analyzed patients' records for cataract surgery in the fellow eye and for any postoperative inflammation lasting more than three months or recurrences after the initial healing.

Twenty-six cases of culture-proven *P. acnes*-associated endophthalmitis after extracapsular cataract surgery were identified. Of these, 12 patients had undergone bilateral cataract surgery. Five patients had undergone cataract surgery after *P. acnes* infection in the fellow eye with a mean follow-up period of 38.6 months (range, five to 84 months). None of these eyes developed prolonged or recurrent postoperative inflammation. Conversely, seven patients had undergone extracapsular cataract surgery in the fellow eye before *P. acnes* infection with a mean follow-up period of 42.3 months (range, 20 to 72 months). None of these noninfected eyes became inflamed during the episode of *P. acnes*-induced inflammation in the contralateral eye.

Although the number of cases in this series is small, the results appear to indicate that the fellow eye is not at great risk for prolonged or recurrent inflammation after *P. acnes*-associated inflammation in the fellow eye. Although this study does not refute the hypothesis that autoimmunity to the lens is an important pathogenic mechanism in this syndrome, it does suggest that inflammation directed against lens antigens in the fellow eye is not an important clinical problem. Nevertheless, alternative pathogenic mechanisms can be conceived. Perhaps an immune response to antigens on the bacteria growing within the eye might induce immunogenic inflammation. Either, or both, antibody-mediated or T cell-mediated mechanisms could be operative. The residual lens proteins would become a passive target of the inflammation initiated by this antibacterial immune response. Since an antigen-specific immune attack against the lens antigens themselves was not involved, the fellow eye would not become the target of inflammation.

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## Glass-Slide Vitrectomy for Use by the Cataract Surgeon

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Occasionally during the course of anterior segment surgery, the posterior lens capsule ruptures and lens fragments become displaced posteriorly. Although this often requires correction in a separate procedure, the cataract surgeon should be able to remove these fragments safely immediately after their displacement into the posterior vitreous space. The main obstacle has been inadequate visualization of the posterior segment of the eye.

The reason for the visual inaccessibility of the posterior segment is the refractive distortion introduced by the corneal surface. Posterior segment surgeons place various types of contact lenses on the eye to eliminate this interface and allow visualization of the retina. These lenses are ordinarily not immediately available to the cataract surgeon.

The same effect can be achieved, however, with a glass microscope slide. At short notice, such slides are usually available sterile. These can be used because the intraoperative eye is an open system; and the pupillary space of an eye in this condition is clear of material protruding into the anterior chamber.

If the posterior lens capsule is ruptured and lens material is lost posteriorly, the anterior vitreous and readily accessible lens material should be removed. The usually available anterior segment vitrectomy unit, modified by the addition of an infusion sleeve, may be used. Vitreous posterior to the iris can be removed safely with this unit, as visualization permits.

A sterile glass slide is placed over the moistened cornea. An applanated circle several mil-

limeters in diameter can be created without difficulty. Because the eye is open, excess fluid escapes from the wound and the intraocular pressure is not unduly high. Because the pupillary space is clear, the corneal endothelium is not jeopardized. Focusing the microscope posteriorly, the retinal surface can be visualized with the coaxial light. An intraocular light probe is not necessary. If lens fragments are noted on the retinal surface, they may be removed. The vitrectomy unit is first moved posteriorly and the formed vitreous in the vicinity is removed. Then the unit is brought close to the lens fragment and gentle suction-only is used. The lens fragment will move into the vitrectomy unit. At this point, the suction is increased to hold the fragment in position, and the instrument is moved anteriorly. Once safely away from the retina, the vitrectomy action can be resumed and the lens material evacuated. If the lens material is cortical, it may even be possible to aspirate it by using high suction only (now that the unit is safely distant from the retinal surface.)

Using this technique will allow the safe removal of lost lens material at the time of the original cataract surgery. Using this procedure will generally obviate the need for later vitrectomy surgery. It will also allow faster rehabilitation of the patient and lower medical costs.

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## Correspondence

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Correspondence concerning recent articles or other material published in *THE JOURNAL* should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

## In Defense of Animal Research

EDITOR:

Gunter K. von Noorden's apologia, "In defense of animal research" (*Am. J. Ophthalmol.* 111:367, March 1991), stated that the activities of animal rights groups have ranged from intimidation and death threats to the infliction of property damage. In truth, these activities represent the extreme, not the range. There are

many individuals who are not totally opposed to animal research and who do not advocate violence, but who feel that the degree of animal suffering in some experiments cannot be justified on the basis of the seriousness of the human condition being studied or on the probability of obtaining findings applicable to the treatment of human disease. For example, highly invasive color vision studies are performed on primates, with whom we share most of our genes. Is this justifiable?

When researchers ascribe some value to the lives of the animals they are using, other than the monetary cost involved in obtaining the animals, we will have come a long way in restoring respect for the sanctity of all life.

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#### EDITOR:

I applaud Dr. von Noorden's attention to animal research; he is a skillful advocate who recommends that we counter activities of animal rights groups by commenting to our patients, "we were able to help your child because of research that is now being threatened by animal rights groups . . ." Dr. von Noorden asks us to become involved in this type of "public education" and "the time to get involved is now!" He provides examples of animal research that, in his opinion, demonstrate "advances that would not have come about without animal research."

As an investigator who has participated in animal (including human) research over the past 25 years, I have had occasion to consider another side of the story, afforded less attention in Dr. von Noorden's editorial. I cannot help but be impressed by some of the reasonable arguments put forward by the Animal Welfare and Animal Rights Groups. Those who argue to limit animal use support their moral philosophy with reasoning that can be compelling. Under certain situations, it is a very complex issue for me, when I consider such matters as the suffering of a primate confined for life to a small cage. It appears easy for us to use primates in research because we are stronger and smarter. When I use primates in my research in this way, I believe I have an especially strong obligation to defend my position thoroughly, beyond informing the public that my way is the right way. I must be as certain as I can that the research is vitally important, that the number of animals is as

limited as possible, that suffering is minimized, and that I have listened carefully to advocates for the animal. Only then may I approach the public. When I approach the public I must be thoroughly prepared to defend myself and my moral philosophy if I come upon an individual who, just as thoughtfully as I, has reached an opposing position.

We should all read Dr. von Noorden's editorial for its advocacy position; then we should all read "Animal Liberation," which so beautifully expresses the advocacy opinion of Peter Singer. Thus informed and educated, the physician can truly be in a position to provide a thoughtful advocacy position to the public. To do less, the physician is little better than the activist he attempts to counter.

I agree with Dr. von Noorden, however, that we must also live in the world as we find it, while we are trying to change it. We need to be prepared, from a practical and political point of view, for the advocates and extremists that we encounter today. At the same time, we should try to do what we can to decrease the polarization of opinion. It is unlikely that the Animal Welfare and Animal Rights Movement will disappear. As educated physicians, I hope we can look at both sides of the question and then begin to forge a compromise position, rather than increase the polarization. If we can provide a compromise position, this is a role of which we can be proud.

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#### EDITOR:

It is unfortunate that Dr. von Noorden does not understand or chooses to dismiss the entire point of why some people oppose this type of research. This type of research typically is defended on the grounds that certain benefits have been accrued by the human species. Pointing to the benefits of one's actions, however, in no way justifies those actions.

The question usually ignored by those who reflexively defend what I will call animal research for simplicity, is the question of morality. Where does one draw the line on how far to go to provide oneself with perceived benefits? As a group, we humans have decided that we will not allow other human beings, regardless of their intellectual or physical status, to be used as mere means to another's ends. Although nonhuman animals appear to be similar in all morally relevant ways to humans, we



have arbitrarily left them out of our sphere of meaningful moral concern in the area of research (as well as in other forms of exploitation). In other words, we have permitted ourselves to do to nonhuman animals what we would never consider doing to ourselves. We tacitly operate under the ethically indefensible and morally reprehensible premise that might makes right. The question is not, therefore, whether benefits can or have been derived from animal research, but whether this is an appropriate way for such a highly developed and intelligent species such as ours to behave.

Many of Dr. von Noorden's arguments or statements are flawed. He naively asserts that "[t]he abuse of experimental animals in biomedical research has become a thing of the past, since adherence to [animal use] policies is mandatory for all recipients of research grants from the National Institutes of Health." That is like saying by passing a law making rape illegal, the problem has ended. How can he be certain that in the thousands of laboratories in this country, no abuse of nonhuman animals is occurring, even by his apparently limited definition?

Dr. von Noorden implies that our understanding of the cause of amblyopia has been furthered only because of animal research. A critical review of the literature, however, does not bear out this point. For example, Claud Worth had made the proper association between amblyopia and strabismus in the 19th century.<sup>1</sup> Although Dr. von Noorden credits animal research with the concept of a sensitive period after birth, earlier ophthalmologists had been recommending early correction of strabismus, and early diagnosis and correction of anisometropia, which indicates that they had known and understood the concept of a sensitive period long before the experimental work using nonhuman animals.<sup>2</sup> Even Dr. von Noorden himself has been critical of animal research when he was considering it only from an academic perspective.<sup>3-5</sup>

When one reviews the situation of amblyopia, it becomes clear that all the work that has been done on nonhuman animals has been based on information derived from human observations.<sup>1,2,5-9</sup> All the hypotheses so far examined by experimental work were considered by physicians in this field years before the experimental work was done. The available history also seems to indicate that there has been essentially no change in concepts or in treatment methods over the last 100 years or more. Contemporary experimental work appears, there-

fore, to have had no significant effect on how amblyopia is treated today.

Dr. von Noorden also implies that the study of human tissue is of value only because of preceding experimental work. This certainly is untrue, even in the cases he cited. Histologic study of enough brain tissue from human patients with amblyopia would lead to an understanding of the anatomic changes just as has been the case with diseases such as Alzheimer's disease. Because of increasing sophistication in our technological methods, we will continue to be able to study the human animal in many ways that will supplant the perceived need to use nonhuman animals in ways that result in significant harm or death to them.

People who argue for equal consideration of the interests of nonhuman animals are not misanthropic. We care about all animals, including humans, and simply want the interests of all to be weighed when decisions are made that involve them. Human beings are not the only creatures deserving of freedom and the pursuit of their interests. Subjugation of others in the name of science does not make it noble or right.

NEDIM C. BUYUKMIHCI, V.M.D.  
Davis, California

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amblyopia. *Trans. Ophthalmol. Soc. U.K.* 99:460, 1979.

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### Reply

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EDITOR:

I appreciate Dr. Lavine's letter and am well aware that not all groups concerned with animal rights are advocating violence. Indeed, I so stated in my editorial. However, I must reject his allegation that researchers do not ascribe any value other than monetary to the lives of animals and that they lack respect for the sanctity of all life. This accusation and the unsupported generalization are unfair since they are directed at all researchers using laboratory animals. Some of this research has made it possible for Dr. Lavine to prevent blindness in his patients and some has actually been of benefit to animals!

Dr. Finkelstein voices his concerns about animal research, some of which I share. I am opposed to animal experiments to gather information that could not equally well be obtained by other and more acceptable means and I abhor abuse of animals. However, I find it difficult to share Dr. Finkelstein's enthusiasm for the writings of Peter Singer, an author who while forcefully espousing the rights of animals, argues in a more recent book that the sanctity of human [*sic*] life cannot rationally be defended.<sup>1</sup>

Dr. Buyukmihci questions the morality and appropriateness of using laboratory animals in general. A response to these complex issues would exceed what is editorially restricted in these pages to a brief reply. He also dismisses the need for animal experiments in amblyopia and strabismus. I do not know on what qualifications Dr. Buyukmihci, a veterinary ophthalmologist, bases his authority to do so. The publications he cites do not support his contentions, nor do they contradict the benefits of animal research, which I mentioned in my editorial. If unconvinced by my views, Dr. Buyukmihci may be interested to know that the International Strabismological Association, which includes 400 leading strabismologists from 44 countries, recognized at its last congress (March 1990) the advances in knowledge and improvement of clinical management of visual disorders in children that has been brought about by animal research, and has endorsed such research in strabismus and amblyopia, provided it is performed under strict guidelines for the protection and humane treatment of laboratory animals.

Just as those arguing for equal consideration of animals may not be misanthropic, researchers may actually be fond of and respect animals, this writer included.

GUNTER K. VON NOORDEN  
*Houston, Texas*

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### A Comparison of Penetrating Keratoplasty to Epikeratoplasty in the Surgical Management of Keratoconus

EDITOR:

In the article, "A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus" by J. D. Goosey, T. C. Prager, C. D. Goosey, E. F. Bird, and J. C. Sanderson (*Am. J. Ophthalmol.* 111:145, February 1991), the authors describe their personal experience with 47 eyes with keratoconus that underwent either epikeratoplasty or penetrating keratoplasty. The authors describe their preoperative inclusion criteria and postoperative refractive and visual results of the patients who underwent either surgical procedure for keratoconus. Our experience has been different than that of the authors with respect to epikeratoplasty inclusion criteria, the use of contact lenses after epikeratoplasty, the effect of epikeratoplasty on glare and contrast sensitivity, rejection rate after penetrating keratoplasty, and the role of epikeratoplasty in the overall treatment of keratoconus.

We agree with the authors' observation that the surgical results of both groups yield a higher percentage of 20/20 best-corrected visual acuity in the patients who underwent penetrating keratoplasty compared to those who had epikeratoplasty. However, the conclusion of the authors may have been biased by their inclusion of nine of their 30 patients (30%) undergoing epikeratoplasty with best-corrected visual acuity preoperatively of 20/50 or worse. Their inclusion criteria, therefore, differed from those of the Nationwide Study,<sup>1</sup> to which our group adhered. Thus, the authors' results are not comparable. The authors do not discuss the need for a contact lens postoperatively in their epikeratoplasty patients who



were contact lens-intolerant preoperatively. We noted in our series that 12 of 33 patients (37%) required a contact lens postoperatively to obtain their best-corrected visual acuity.<sup>2</sup> Therefore, epikeratoplasty does not obviate the need for contact lenses postoperatively, which the authors fail to point out. Although the authors discuss the quality of vision in the epikeratoplasty patients as being reduced because of residual irregularities in Bowman's membrane, there is no discussion of the differences in glare and contrast sensitivity testing between these two procedures with comparable Snellen visual acuity. We have found that the performance for these two factors is worse in the epikeratoplasty patients, compared to the penetrating keratoplasty patients for keratoconus.<sup>3</sup>

Epikeratoplasty has been favored in those patients who meet inclusion criteria to avoid the risks of endothelial rejection, which ultimately leads to a failed transplant in 7% to 10% of postoperative penetrating keratoplasty patients for keratoconus. Our long-term results verify these observations.<sup>4</sup> The authors do, however, report a 31% first-year rejection rate, which appears to be excessively high, although all patients were apparently treated successfully with topical immunosuppression.

Based on the experience of 47 operations for keratoconus, the authors imply a major role for epikeratoplasty in the management of keratoconus. In our series of 746 eyes, spectacles or contact lenses were used in 554 eyes (74%); 156 eyes (21%) had penetrating keratoplasty; and only 36 eyes (4%) had epikeratoplasty. Epikeratoplasty has a limited role in the management of keratoconus, confined to the patient who is contact lens-intolerant and has best-corrected visual acuity of 20/40 or better and no apical scarring.

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## Reply

### EDITOR:

Before the publication of our article, there was only limited information comparing the efficacy of epikeratoplasty and penetrating keratoplasty in the treatment of keratoconus. Our article was intended to provide a more extensive comparative analysis of these two procedures performed by the same surgeon in patients with keratoconus.

Our investigation showed that both surgical groups had the same percentage of eyes (93%) with best-corrected visual acuity of 20/40 or better. A further analysis of visual acuity showed a significantly higher percentage of patients with 20/20 best corrected acuity in the penetrating keratoplasty group (73%) than epikeratoplasty group (24%) one year after surgery. Our inclusion of patients with 20/50 or better preoperative visual acuity in the epikeratoplasty group when all of the eyes with penetrating keratoplasty had visual acuity worse than 20/50 does not necessarily lead to a bias in the results. The postoperative findings are valid because both groups were screened for retinal disease and other abnormalities and have the same visual potential.

Our research protocol was not designed to be a direct comparison to the Nationwide Epikeratophakia Study. Lembach, Lass, and Foulks are correct in noting that our visual inclusion of 20/50 or better for the epigraft population is one line worse than the Nationwide Epikeratophakia Study criterion of 20/40. However, other marked differences separate the two studies. As detailed in the methods section, our epigraft lenticuli were prepared without lyophilization and had a central thickness of 0.2 mm. In contrast, the lenticuli

used in the Nationwide Epikeratophakia Study were lyophilized and had a central thickness of 0.3 mm. We believe the use of nonlyophilized tissue facilitates postoperative recovery because of faster reepithelization. None of our patients had an epigraft failure because of a persistent epithelial defect. The thinner central thickness of our grafts results in a thinner overall cornea, which may partially explain the higher percentage of patients (93%) with best-corrected visual acuity of 20/40 or better in our study relative to that found in the Nationwide Epikeratophakia Study (78%). Other confounding factors include many surgeons with differing degrees of experience with epikeratophakia in the Nationwide Epikeratophakia Study.

Tables 2 and 3 in our article highlight visual acuity results over time for spectacle and contact lenses. These results show that visual acuity with contact lenses was superior to that with spectacles in eyes that had undergone both epikeratoplasty and penetrating keratoplasty. This does not imply that either surgical procedure obviates the need for postsurgical use of contact lenses. On the contrary, most of our patients in both groups used contact lenses because they had superior vision with them.

The 31% (5/16) rate of graft reactions we encountered in eyes that underwent penetrating keratoplasty is well within the results of published reports, which range from 6% to 56% in keratoconus populations. Although our graft reaction rate seems high to Lembach, Lass, and Foulks and although it may be a consequence of a relatively small sample size, this does not mitigate the potentially serious risk that immune reactions may pose after penetrating keratoplasty. We agree with Lembach, Lass, and Foulks that the primary method of visual rehabilitation in such patients is a proper contact lens fit. The Hermann Eye Center is a major referral center for keratoconus patients and most are successfully treated with contact lenses. However, the 47 eyes described in our

study were contact lens-intolerant and required surgical treatment. Surgical intervention, according to Lembach, Lass, and Foulks in a tertiary referral center, was performed in approximately one of every four eyes (192/746). This does not suggest a limited role for epikeratoplasty because 20% of the 192 eyes in their own series underwent epikeratoplasty.

We hope that the important questions raised by Lembach, Lass, and Foulks will stimulate interest in the use of epikeratoplasty as a viable alternative for selected keratoconus patients.

JOHN D. GOOSEY, M.D.  
THOMAS C. PRAGER, PH.D.  
CLAIRE B. GOOSEY, M.S.  
EUGENE F. BIRD, M.D.  
JAMES C. SANDERSON, M.D.  
*Houston, Texas*

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### **Therapeutic Ultrasound for the Treatment of Glaucoma—Correction**

#### **EDITOR:**

In our article, "Therapeutic ultrasound for the treatment of glaucoma" (*Am. J. Ophthalmol.* 111:327, March 1991), we omitted acknowledgement of the contribution of Joseph G. Feghali, M.D., as principal investigator for the University Eye Center, Department of Ophthalmology, West Virginia University, Health Sciences Center, Morgantown, West Virginia.

RONALD H. SILVERMAN, Ph.D.  
BARBARA VOGELSANG, M.D.  
MARK J. RONDEAU  
D. JACKSON COLEMAN, M.D.  
*New York, New York*

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## BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

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**Advances in Ophthalmic Plastic and Reconstructive Surgery.** By Stephen L. Bosniak and Byron C. Smith. Philadelphia, Pergamon Press, 1990. 288 pages, index, illustrated. \$82.50

Reviewed by KEITH D. CARTER  
*Iowa City, Iowa*

The aim of this text is to describe previous experiences, outline current techniques for anophthalmic socket rehabilitation, and highlight some possible future developments.

The opening chapters cover the history of artificial eyes and facial prosthetics. This is a useful review of the development of ocular prosthetics from its early years in Europe through the formative years in the United States, which led to the formation of the American Society of Ocularists. The description of ocular prosthetic construction includes the materials used and gives insight on the artistic ability needed for success. Several techniques are described for the modification of prostheses that can be used to correct structural problems in anophthalmic sockets without surgery.

Many surgical procedures are also described that are directed toward the correction of complications related to the anophthalmic socket, ranging from the repair of eyelid laxity and superior sulcus deformities to contracted sockets. Motility implants such as the traditional sphere implant wrapped in Gore-Tex or the universal implant provide practical surgical alternatives. The most recent integrated implant, consisting of hydroxyapatite, is described with a brief history on its development. Orbital volume augmentation with autogenous material such as dermis-fat grafts or alloplastic material such as room temperature vulcanizing Silastic and silicone implants is described.

The text will serve as an excellent resource for any clinician who cares for these patients with anophthalmic socket problems. The various challenges are addressed, and methods for their correction are discussed. It is clear that input from many disciplines is needed to solve the problems such patients encounter.

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**Visual Impairment: An Overview.** By Ian L. Bailey and Amanda Hall. New York, American Foundation for the Blind, 1990. Softcover, 49 pages. \$12.95

Reviewed by FRANK J. WEINSTOCK  
*Canton, Ohio*

The causes of visual impairment are often poorly understood by those afflicted, by those who take care of such patients, and by friends and family. The ophthalmologist, as well as the non-ophthalmologist, has an obligation to provide the information that patients and those around them need to help them to adjust to visual loss. This information includes an understanding of the eye, the causes of visual loss, and the optical treatments available. The patient and family should also be informed about reactions to loss of vision, how visual impairment relates to independent living, and what assistance and resources are available.

This monograph deals with all of these topics. It is addressed to the public, but is of interest not only to the patient but to ophthalmologists and their office staff. It should be required reading for the office staff and should be made available to patients and families by means of a copy in the reception area and by informing patients of its availability through the American Foundation for the Blind.

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### Books Received

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**California Resource Directory for the Blind and Visually Impaired.** By Howard Schatz, Margaret M. Stolarczuk, H. Richard McDonald, and Robert N. Johnson. California, The Retina Research Fund, 1990. 122 pages, illustrated. \$19

This pleasingly put together book is full of useful information. Gary Laufman's eye-catching photographs make their statements with unusual clarity. This book should serve as a model for similar resource directories in other states.

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**Vascular Disorders of the Ocular Fundus.** By Rodney Grey. Stoneham, MA, Butterworth-Heinemann, 1991. 118 pages, index, illustrated. \$85

This is a short text with some nice pictures that might serve as an introduction to the subject for an ophthalmology resident.

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## Obituary

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### TOICHIRO KUWABARA

1920-1991

Toichiro Kuwabara, one of America's premier ophthalmic pathologists, died on April 2, 1991, of cardiovascular insufficiency at the age of 71 years. Thus ended a brilliant career in which a young pathologist from Japan became an eminent research scientist in America. His many contributions included studies on lipid keratopathy, diabetic retinopathy, photic damage to the retina, diabetic cataracts, genetic diseases of the eye, and a host of other ocular abnormalities. No less important was the major role he played in introducing electron microscopy and novel histochemical techniques to eye research. In the laboratory he set uncompromisingly high standards for himself and for his staff.

Dr. Kuwabara was born in 1920 on the island of Shikoku, Japan, the eldest son of a prominent medical family. He received his medical school training at Kyushu University, where he graduated in 1944 and later obtained a Ph.D. degree (Metastatic Mechanism of Lung Cancer), in preparation for a planned career in general pathology. In 1947, while an instructor in pathology at Kyushu University, he married Dr. Chishiko Takeuchi, who was a recent graduate of the Osaka Medical School. In 1952, we recruited Dr. Kuwabara for a trial year in the Howe Laboratory of Ophthalmic Research at Harvard Medical School and the Massachusetts Eye and Ear Infirmary.

He arrived in this country with little more than a satchel, a broad smile, and meager familiarity with the English language. Nevertheless, he soon became a productive member in the small family of clinical and basic scientists dedicated to eye research. Together we explored fat metabolism in the cornea where his talent for tissue processing and his uncompromising perfectionism proved him indispensable. Unfortunately, the McCarran Act required his return to Japan and a wait of several long months before he could return as a permanent resident. He did eventually return, this time with his wife and two little girls, and immediately reactivated his studies on aberrant lipogenesis. This project opened up an entirely new field not only in eye research but in atheromatosis and fatty degeneration elsewhere in the body.

Then one of those serendipitous observations



Toichiro Kuwabara

1920-1991

caused a redirection of research. A piece of retina was incidentally trypsinized along with the corneal preparation. When this retina was subsequently stained by the periodic acid-Schiff, it revealed for the first time the cellular topography of retinal capillaries. Important in itself as an anatomic discovery, this finding came to have crucial significance in elucidating the pathogenesis of diabetic retinopathy; the mural cells (pericytes) of the retinal capillaries are the target cells in diabetes. The Kuwabara trypsin digestion technique became the universal procedure for studying retinal blood vessels.

The foregoing lipid and retinal studies were major directions of Dr. Kuwabara's research in the Howe Laboratory but were only part of his extensive and innovative contributions, all of which established his authority in understanding the normal and pathologic eye. For all these accomplishments, he was honored with the Hektoen Silver Medal of the American Medical Association (1960), the New England Ophthalmic Society Award (1962), the Friedenwald Award (1968), the Research to Prevent Blindness Trustees' Award (1970), the Alcon Re-



search Institution Award (1982), the Senior Investigator Award of Research to Prevent Blindness (1991), and the honor of being a much sought-after collaborator in ophthalmic research and, often, research outside of ophthalmology. Promotions at the Harvard Medical School followed in due course to the title of professor of pathology in the Department of Ophthalmology (1971).

In 1972, with administrative changes in the Howe Laboratory pending, Dr. Kuwabara and a group of several senior investigators left Boston to join the new National Eye Institute. For the next 17 years, Dr. Kuwabara was chief of the Laboratory of Ophthalmic Pathology at the National Eye Institute. The opportunity for collaborative research in the Institute is evident in Dr. Kuwabara's continuing publications for these years. The total number of papers authored or coauthored by Dr. Kuwabara is more than 200, covering a wide range of subjects.

It was in the zenith of this later period that Dr. Kuwabara developed the cardiovascular

problems that ultimately took his life. He developed an aortic aneurysm and coronary occlusion that required two major operations and prolonged convalescence. Despite recurrent decompensation, his mental facilities remained alert as did his determination to continue to work energetically. With his usual fortitude he accepted in 1989 the challenge to set up an ophthalmic pathology laboratory at the University of Indiana. This was already a functioning laboratory under his direction when, on returning home after work on the afternoon of April 2, he went into his garden, did some planting and weeding, then, apparently, stretched out on the grass and passed away; a merciful ending for one who would have found idle invalidism worse than death.

Dr. Kuwabara leaves his wife, four daughters, two brothers, a sister (in Japan), and innumerable grateful friends and associates whose lives he has abundantly enriched.

DAVID G. COGAN

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## ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

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**Preoperative laboratory screening in healthy Mayo patients: Cost-effective elimination of tests and unchanged outcomes.** Narr, B. J.\*, Hansen, T. R., and Warner, M. A.: Mayo Clin. Proc. 66:155, 1991.

### PREOPERATIVE ASSESSMENT, LABORATORY TESTS, COST EFFECTIVENESS

Preoperative assessment of patients usually consists of a medical history, a physical examination, and laboratory tests. Screening laboratory tests, however, may fail to reveal pathologic conditions, or they may detect clinically unimportant abnormalities in healthy patients. Moreover, abnormalities detected by these tests may not be recorded or pursued. It is not clear whether preoperative laboratory tests are cost-effective.

The authors reviewed the results of preoperative screening laboratory tests in asymptomatic healthy patients who underwent surgical procedures at the Mayo Clinic in 1988. Substantially abnormal results were found in 160 of 3,782 patients. All such abnormalities involved five tests: glucose, potassium, platelet count, hemoglobin, and aspartate aminotransferase. Thirty of the abnormal test results were predictable on the basis of the history or physical examination. The abnormal test results prompted further assessment in 47 patients. No surgical procedure was delayed and no association was noted between adverse outcome and any preoperative laboratory abnormality. Because of the findings in this study, and similar studies from other institutions, preoperative laboratory screening tests are no longer required for healthy patients at the Mayo Clinic.—Michael A. Kass

\*Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905.

**Medical educators' views on medical education reform.** Cantor, J. C.\*, Cohen, A. B., Barker, D. C., Shuster, A. L., and Reynolds, R. C.: JAMA 265:1002, 1991.

### MEDICAL EDUCATION

To determine whether medical educators perceive a need for change in medical student education, the authors analyzed data from a 1989 survey of 1,369 respondents from all United States schools of allopathic medicine. Within each school, the authors attempted to obtain information from the dean, the associate dean for either academic affairs or student affairs, two basic science chairmen, and four clinical chairmen. In addition, randomly selected affairs or student affairs, two basic science chairmen, and four clinical chairmen. In addition, randomly selected members of the basic science faculty and the clinical faculty were included. Only full-time faculty who held the rank of assistant professor or higher and who spent some portion of their time teaching medical students were eligible to participate. More than 60% of the deans, associate deans, and clinical faculty believed that medical student education needed fundamental or thorough reform. In contrast, more than 50% of the basic science faculty stated that medical student education required only minor changes. At least 79% of the educators voiced support for six specific reforms including the following: developing a system for evaluating and rewarding faculty for teaching excellence; increasing the integration between the basic sciences and clinical medicine; developing testing mechanisms to evaluate problem solving skills; decreasing the number of large lectures and increasing student time for independent study and interaction with faculty; moving clinical education from inpatient to ambulatory and community settings; and placing greater emphasis on general medical education of students and relying more heavily on residencies for specialty training. Many of the educators believed that it will be difficult to implement some of these reforms despite a broad consensus for change.—Michael A. Kass

\*The Robert Wood Johnson Foundation, Office of Health Statistics and Analysis, P.O. Box 2316, Princeton, NJ 08543-2316.



**The effect of dexamethasone on glycosaminoglycans of human trabecular meshwork in perfusion organ culture.** Johnson, D. H.\*, Bradley, J. M. B., and Acott, T. S.: *Invest. Ophthalmol. Vis. Sci.* 31:2568, 1990.

**CORTICOSTEROID, TRABECULAR MESHWORK, GLYCOSAMINOGLYCANS**

Corticosteroid administration may increase intraocular pressure and decrease outflow facility in susceptible individuals. Although corticosteroid-induced glaucoma has been recognized for over 30 years, the pathogenesis of this condition is unknown. In order to study this problem, twenty pairs of human eyes were placed in perfusion organ culture. One eye of each pair was administered 500 nM of dexamethasone in addition to the culture medium; the fellow eye was administered culture medium only. Labeled glucosamine and sulfate were added to the medium for the final 48 hours of culture. The trabecular meshwork was then dissected and the glycosaminoglycans were isolated and subjected to sequential enzymatic degradation. Active labeling of hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate, and heparan sulfate was found in both control and corticosteroid treated eyes. The dexamethasone-treated eyes had a mean 92% increase in the rate of labeled glucosamine incorporation in the undigestible glycosaminoglycan fraction after 14 to 21 days of treatment. This change was not apparent in eyes treated for only seven days. In this preliminary study, dexamethasone appeared to cause a time-dependent increase in the undigestible glycosaminoglycan incorporation profile in human trabecular meshwork. This may explain corticosteroid-induced reductions in outflow facility.—Michael A. Kass

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**Microaerosol formation in noncontact "air-puff" tonometry.** Britt, J. M., Clifton, B. C., Barnebey, H. S., and Mills, R. P.\*: *Arch. Ophthalmol.* 109:225, 1991.

**NONCONTACT TONOMETRY, MICROAEROSOL FORMATION, POTENTIAL CONTAMINATION**

Viruses, including the human immunodeficiency virus, have been isolated from the tears of infected individuals. Although tears have not been implicated in the spread of human immunodeficiency virus, concern about the possible transmission of viral infections during contact tonometry has generated recommendations for minimizing this risk through sterilization of tonometer tips. A number of authorities have suggested that noncontact or air-puff tonometry may be a safer alternative to contact tonometry because no apparent contact exists between the instrument and the eye. A camera and a flash were electrically coupled to two different models of noncontact tonometers to photograph the corneal profile and the tear layer during noncontact tonometry. In most eyes, the airjet caused tear film dehiscence and microaerosol formation. This was best seen when the tear film was stained with fluorescein. The tear droplets reached the tonometer and may reach medical personnel. Thus noncontact or air-puff tonometry may not be aseptic as previously presumed.—Michael A. Kass

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**The Lens Opacities Case-Control Study. Risk factors for cataract.** Leske, M. C.\*, Chylack, Jr., L. T., and Wu, S.-Y., The Lens Opacities Case-Control Study Group: *Arch. Ophthalmol.* 109:244, 1991.

**CATARACT FORMATION, RISK FACTORS, VITAMIN INTAKE, DIABETES**

The Lens Opacities Case-Control Study evaluated risk factors for age-related nuclear, cortical, posterior subcapsular, and mixed cataracts. The 1380 participants were ophthalmology outpatients, aged 40 to 79 years, classified into the following groups: posterior subcapsular only, 72 patients; nuclear only, 137 patients; cortical only, 290 patients; mixed cataract, 446 patients; and controls, 435 patients. In polychotomous logistic regression analyses, low education increased risk (odds ratio [OR] = 1.46) and regular use of multivitamin supplements decreased risk (OR = 0.63) for all cataract types. Dietary intake of riboflavin, vitamins C, E, and carotene, which have antioxidant poten-

tial, was protective for cortical, nuclear, and mixed cataract; intake of niacin, thiamine, and iron also decreased risk. Similar results were found in analyses that combined the antioxidant vitamins (OR = 0.40) or considered the individual nutrients (OR = 0.48 to 0.56). Diabetes increased risk of posterior subcapsular, cortical, and mixed cataracts (OR = 1.56). Oral steroid therapy increased posterior subcapsular cataract risk (OR = 5.83). Females (OR = 1.51) and nonwhites (OR = 2.03) were at increased risk only for cortical cataract. Risk factors for nuclear cataract were a nonprofessional occupation (OR = 1.96), current smoking (OR = 1.68), body mass index (OR = 0.76), and occupational exposure to sunlight (OR = 0.61). Gout medications (OR = 2.48), family history (OR = 1.52), and use of eyeglasses by age 20 years, which is an indicator of myopia (OR = 1.44), increased risk of mixed cataract. The results support a role for the nutritional, medical, personal, and other factors in cataractogenesis. The potentially modifiable factors suggested by this study merit further evaluation.—Authors' abstract

\*Division of Epidemiology, Department of Preventive Medicine, SUNY at Stony Brook, HSC, L3-099, Stony Brook, NY 11794-8036.

**Lenses of diabetic patients "yellow" at an accelerated rate similar to older normals.** Lutze, M.\*, and Bresnick, G. H.: *Invest. Ophthalmol. Vis. Sci.* 32:194, 1991.

#### DIABETES, ACCELERATED AGING OF THE LENS

Lens absorption of short-wavelength light increases with age, thereby causing the lens to appear yellow. In the normal population, psychophysical and physical measurements of lens absorption demonstrate a linear increase in lens yellowing until approximately 60 years of age, after which the process accelerates. The authors employed a psychophysical technique to measure the relative amounts of short-wavelength light absorbed by the lens in a cohort of young type 1 diabetic patients and normal controls. In the diabetic subjects, the lenses yellowed or aged at an accelerated rate that was similar to the rate seen in normal controls over

the age of 60 years. The authors propose that diabetic individuals and older normal individuals have increased plasma glucose levels. This leads to accelerated glycosylation of lens proteins which in turn causes increased lens yellowing.—Michael A. Kass

\*Visual Sciences Center, University of Chicago, 939 E. 57th St., Chicago, IL 60637.

**Long-term survival rate after vitreous surgery for complications of diabetic retinopathy.** Gollamudi, S. R., Smiddy, W. E.\*, Schachat, A. P., Michels, R. G., and Vitale, S.: *Ophthalmology* 98:18, 1991.

#### DIABETIC RETINOPATHY, VITREOUS SURGERY, SURVIVAL RATE

The survival rate after vitreous surgery for complications of diabetic retinopathy was studied in 552 consecutive patients who underwent operations between 1979 and 1984. The 5-year postoperative survival rate was 74.7%. Factors associated with a lower survival rate included older age, older age at diagnosis of diabetes, history of renal disease, and a longer duration of diabetes. Factors unrelated to survival rate included insulin treatment, sex, and anatomic and visual outcome. Improved management of systemic diabetic complications has improved survival rates, a finding reflected in the relatively high rate of long-term survival after diabetic vitrectomy.—Authors' abstract

\*Bascom Palmer Eye Institute, University of Miami School of Medicine, 900 N.W. 17th St., Miami, FL 33136.

**Visual acuity in infants after vitrectomy for severe retinopathy of prematurity.** Quinn, G. E.\*, Dobson, V., Barr, C. C., Davis, B. R., Flynn, J. T., Palmer, E. A., Robertson, J., and Trese, M. T.: *Ophthalmology* 98:5, 1991.

#### RETINOPATHY OF PREMATURE, RETINAL DETACHMENT, VITRECTOMY

During the course of the multicenter trial of cryotherapy for retinopathy of prematurity, 98



infants (129 eyes) developed total retinal detachment before the 1-year examination. Fifty-three infants (71 eyes) underwent surgical repair of the retina, including vitrectomy. Forty-five infants (58 eyes) did not undergo retinal detachment surgery. The decision to undergo surgery for retinal detachment was nonrandomized and was not part of the clinical trial. Of the infants who underwent surgery, only one child had pattern vision at the lowest measurable threshold after vitrectomy. None of the remaining eyes that underwent retinal detachment surgery and none of the eyes that did not undergo surgery showed evidence of pattern vision, using an acuity card assessment. The poor visual outcome in this series underscores the importance of preventing retinal detachment in retinopathy of prematurity.—Michael A. Kass

\*Division of Pediatric Ophthalmology, Children's Hospital of Philadelphia, One Children's Center, Philadelphia, PA 19104.

**Incidence and characteristics of retinopathy of prematurity in a low-income inner-city population.** Charles, J. B., Ganthier, Jr., R., and Appiah, A. P.\*: *Ophthalmology* 98:14, 1991.

#### RETINOPATHY OF PREMATURITY, INNER-CITY POPULATION

The authors have prospectively studied the incidence and nature of retinopathy of prematurity (ROP) in 159 consecutive preterm infants at an institution serving a predominantly black and Hispanic, low-income, inner-city population. Overall, ROP developed in 73 (46%) of the 159 patients. However, ROP developed in 54 (72%) of 75 patients with birth weight under 1200 grams. Significant high-risk factors observed were low birth weight ( $P < 0.001$ ), short gestation period ( $P < 0.001$ ), and extended supplemental oxygen administration period ( $P < 0.001$ ). Other significant factors were the presence of intraventricular hemorrhage ( $P < 0.01$ ) and respiratory distress syndrome ( $P < 0.01$ ). An additional factor observed to be significant for the development of severe ROP (stages III–V) was sepsis ( $P < 0.01$ ). Race and maternal history of substance abuse were not

found to be significant factors. The unusually high incidence (72%) of ROP in low birth weight infants found in this study may be due to limited prenatal care and other maternal factors such as inadequate nutrition.—Authors' abstract

\*Alpha Eye Center, 2160 Capital Circle, N.E., Tallahassee, FL 32308.

**Human retinal pigment epithelium contains two distinct species of superoxide dismutase.** Newsome, D. A.\*, Dobard, E. P., Liles, M. R., and Oliver, P. D.: *Invest. Ophthalmol. Vis. Sci.* 31:2508, 1990.

#### SUPEROXIDE DISMUTASE, ANTIOXIDANT ACTIVITY, RETINAL PIGMENT EPITHELIUM

The retinal pigment epithelium has an oxygen-rich environment and is thus exposed to oxygen-generated free radicals. These free radicals, including superoxide anions, can alter biologically active molecules and may contribute to age-related changes in the retinal pigment epithelium and retina. The superoxide dismutases are metalloenzymes that protect against oxygen toxicity. Previous studies of nonhuman retinal pigment epithelium have either probed specifically for copper-zinc-containing superoxide dismutase or have not distinguished between the copper-zinc enzyme and the enzyme containing manganese. Enzymatic assays and immunologic probes were used in vivo and in vitro to demonstrate that human retinal pigment epithelium contains both copper-zinc superoxide dismutase and manganese superoxide dismutase. The copper-zinc superoxide dismutase has a diffuse cytosolic distribution, whereas the manganese form is located primarily in the mitochondria. The role of these enzymes in protecting the choroid and retina against oxidative damage and aging processes is not well understood. It seems likely that both enzymes are important in scavenging superoxide radicals generated in mitochondria as a byproduct of oxygen metabolism.—Michael A. Kass

\*Sensory and Electrophysiology Research Unit, Touro Infirmary 1401 Foucher St., New Orleans, LA 70115.

**Differentiation of detached retina and vitreous membrane with color flow Doppler.** Wong, A. D.\*, Cooperberg, P. L., Ross, W. H., and Araki, D. N.: *Radiology* 178:429, 1991.

**RETINAL DETACHMENT, VITREOUS MEMBRANES, COLOR FLOW DOPPLER**

In most cases, it is easy to distinguish retinal detachment from vitreous membranes on clinical examination or high-resolution real-time sonography. However, in rare cases this differentiation may be difficult. Patients who had signs or symptoms suggestive of retinal detachment were examined using a standard ultrasound technique as well as color Doppler. The color Doppler scale and filter were set to detect low rates of blood flow in retinal vessels. Seven eyes had retinal detachment, and in all of these blood flow was detectable in at least one portion of the detached retina. Seventeen eyes had vitreous hemorrhages or membranes and in fifteen of these no blood flow was detected. However, in two diabetic patients with vitreous membranes and no retinal detachment, blood flow was detected in the neovascular membranes. The authors concluded that, with the exception of diabetic patients, they were able to distinguish retinal detachment from vitreous membranes using high-resolution color flow Doppler.—Michael A. Kass

\*Department of Radiology and Ophthalmology, St. Paul's Hospital, 1081 Burrard St., Vancouver, BC, Canada V6Z 1Y6.

**The ocular ischemic syndrome. III. Visual prognosis and the effect of treatment.** Sivalingam, A.\*, Brown, G. C., and Magargal, L. E.: *Int. Ophthalmol.* 15:15, 1991.

**CAROTID ARTERY STENOSIS, OCULAR ISCHEMIC SYNDROME**

It is estimated that 5% of patients with marked carotid artery stenosis also have the ocular ischemic syndrome. This syndrome consists of rubeosis iridis, narrowed retinal arteries, mid-peripheral retinal hemorrhages and posterior segment neovascularization. The authors reviewed the records of 52 consecutive patients with the ocular ischemic syndrome seen between 1978 and 1985. On initial exami-

nation, 43% of affected eyes had a visual acuity of 20/20 to 20/50, whereas 37% were counting fingers or worse. By the end of one year, only 24% remained in the 20/20 to 20/50 visual acuity group, whereas 58% were counting fingers or worse. The presence of rubeosis iridis was an indicator of poor visual prognosis; 97% of eyes with rubeosis had vision of counting fingers or worse at the end of one year. The authors were unable to demonstrate that carotid endarterectomy and superficial temporal artery to middle cerebral artery bypass were of benefit in stabilizing or improving vision in individuals with the ocular ischemic syndrome.—Michael A. Kass

\*Retina Vascular Unit, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA.

**Eye injuries among pennant squash players and their attitudes towards protective eyewear.** Genovese, M. T., Lenzo, N. P., Lim, R. K., Morkel, D. R., and Jamrozik, K. D.\*: *Med. J. Aust.* 153:655, 1990.

**SQUASH, EYE INJURIES, PROTECTIVE EYEWEAR**

A questionnaire on eye injuries and attitudes towards protective eyewear was conducted among 165 expert squash players. The incidence of eye injuries in the sample was found to be 17.5 per 100,000 playing hours, with a significant proportion of the players (26%) indicating they had suffered at least one eye injury. Injuries were more commonly caused by racquets than by squash balls. A large proportion of those injured (63%) consulted a doctor with approximately one-third of the injured players (or 5% of the total sample) having been admitted to a hospital for an eye injury. Only 8% of the sample used appropriate protective eyewear, with an additional 2% believing their prescription lenses afforded protection. The main reason given for using protective eyewear was previous injury to themselves or others. Neither doctors nor media promotion influenced players to use protective eyewear. Most respondents believed the use of eyewear to be beneficial, but fewer than half believed that eyewear should be made compulsory for all players. Only 6% of the players said that they would give up squash if the use of eyewear were made compulsory.—Michael A. Kass



\*Unit of Clinical Epidemiology, M. Block, Queen Elizabeth II Medical Centre, Nedlands, Western Australia 6009.

**Review of lacrimal gland lesions.** Shields, C. L.\*, and Shields, J. A.: *Trans. Pa. Acad. Ophthalmol. Otolaryngol.* 42:925, 1990.

#### LACRIMAL GLAND LESIONS, INFLAMMATORY MASSES, LYMPHOID TUMORS

Lesions of the lacrimal gland fossa account for 5% to 13% of all biopsied orbital masses. These lesions can originate from the epithelial elements of the lacrimal gland or from the nonepithelial elements. In most series, approximately 50% of lacrimal fossa tumors are of epithelial origin and 50% are of nonepithelial origin. The authors reviewed 142 lacrimal gland lesions biopsied over a 25-year period. In this series, 78% (111 of 142 lacrimal gland lesions) were of nonepithelial origin and only 22% (31 of 142 lacrimal gland lesions) were primary epithelial neoplasms. The nonepithelial lesions included 71 inflammatory masses (64%) and 16 lymphoid tumors (14%), and the epithelial lesions included two dacryops (6%), four pleomorphic adenomas (12%), and one malignant epithelial tumor (4%). This series was restricted to lesions that were biopsied or surgically excised. Therefore, the true incidence of inflammatory lesions and nonepithelial tumors was probably even higher than the 78% reported; because many inflammatory lesions were managed medically and not biopsied.—Michael A. Kass

\*Ocular Oncology Service, Wills Eye Hospital, Ninth and Walnut Sts., Philadelphia, PA 19107.

**Systemic sulfonamides as a cause of bilateral, anterior uveitis.** Tilden M. E., Rosenbaum J. T.\*, and Fraunfelder, F. T.: *Arch. Ophthalmol.* 109:67, 1991.

#### SULFONAMIDE TREATMENT, ANTERIOR UVEITIS

Between September 1976 and May 1989, 12 cases of uveitis attributed to the systemic use of sulfonamide derivatives were reported to the National Registry of Drug-Induced Ocular Side Effects and the US Food and Drug Administra-

tion. We evaluated these reports in addition to one case previously reported in the literature and one patient seen at the Uveitis Clinic, Oregon Health Sciences University, Portland. The patients' median age was 34 years. Twelve of 14 patients were treated with trimethoprim-sulfamethoxazole. All patients for whom the location of the eye disease was specified presented with an iritis. Six reports included a description of ocular symmetry, with all patients having bilateral inflammation. Of the nine patients for whom data on the duration of drug use was available, seven experienced adverse effects within 8 days of beginning trimethoprim-sulfamethoxazole therapy and four showed effects within 24 hours. Three patients had histories of rechallenge with trimethoprim-sulfamethoxazole, and in each case acute iritis recurred within 24 hours of reinstitution of therapy. Five patients had additional evidence of an adverse reaction manifested as Stevens-Johnson syndrome, erythema multiforme, diffuse macular or vesicular rashes, stomatitis, glossitis, conjunctival and scleral injection, and granulomatous hepatitis. The consistent presentation including bilateral, anterior inflammation and the recurrence with rechallenge strongly indicate a cause-effect relationship. Although uveitis secondary to sulfonamides is a rarely diagnosed clinical event, recognition of the distinct presentation of this entity is important in the differential diagnosis of uveitis.—Authors' abstract

\*Oregon Health Sciences University, 3181 S.W. Jackson Park Rd., Portland, OR 97201.

**Visual disturbances in man as a result of experimental and occupational exposure to dimethylethylamine.** Stahlbom, B., Lundh, T., Floren, I., and Akesson, B.\*: *Br. J. Ind. Med.* 48:26, 1991.

#### DIMETHYLETHYLAMINE, EYE IRRITATION, VISUAL DISTURBANCES, CORNEAL EDEMA

Tertiary aliphatic amines are widely used as catalysts in foundry and polyurethane foam manufacturing operations. Dimethylethylamine and similar agents are known to cause ocular irritation. Four volunteers were exposed to air concentrations of dimethylethylamine of 40 to 50 mg/m<sup>3</sup> of body surface. All subjects

developed ocular irritation, subjective visual disturbances and corneal edema after three to seven hours of exposure. The signs and symptoms faded within one to three hours after the subjects were removed from exposure. These concentrations of dimethylethylamine are similar to those found in a number of industrial settings. Exposure to dimethylethylamine caused no permanent ocular injury, but the corneal edema could predispose the workers to industrial accidents. Measurement of corneal thickness showed a slight but consistent increase during experimental studies after exposure to as low a concentration as 10 mg of dimethylethylamine per m<sup>3</sup> body surface.—Michael A. Kass

\*Department of Occupational and Environmental Medicine, University Hospital S-221 85 Lund, Sweden.

**Acquired pendular nystagmus in toluene addiction.** Maas, E. F., Ashe, J., Spiegel, P., Zee, D. S., and Leigh, R. J.\*: *Neurology* 41:282, 1991.

#### GLUE SNIFFING, TOLUENE, PENDULAR NYSTAGMUS

Toluene is a widely abused organic solvent. Chronic inhalation of glue containing toluene is toxic to the central nervous system and leads to a progressive neurologic syndrome characterized by cognitive impairment, cerebellar ataxia, pyramidal tract signs, anosmia, and deafness. Patients addicted to toluene may also have visual impairment caused by optic atrophy as well as abnormal eye movements including nystagmus, ocular flutter, and opsoclonus. Four patients chronically addicted to sniffing glue containing toluene were studied. All four patients had acquired pendular nystagmus with horizontal and vertical components. One of the patients also had saccadic oscillations. The authors postulate that the pendular nystagmus may be a manifestation of a disturbance in brainstem-cerebellar connections secondary to the toxic effect of toluene on white matter. Toluene abuse should be included in the differential diagnosis of patients with acquired pendular nystagmus.—Michael A. Kass

\*Department of Neurology, University Hospitals of

Cleveland, 2074 Abington Rd., Cleveland, OH 44106.

**A surgically implanted elastic band to restore paralyzed ocular rotations.** Bicas H. E. A.\*: *J. Pediatr. Ophthalmol. Strabismus* 28:10, 1991.

#### PARALYTIC STRABISMUS, ELASTIC BAND

Five patients with ocular deviations of up to 70 degrees and limitation of movement caused by a paralytic horizontal rectus muscle were treated with a surgical technique in which the affected eye was bound to the orbit by an elastic silicone band. The purpose was to obtain fixation of the eye in an overcorrected position (for example, in adduction if the patient had an exodeviation). After surgery, contraction of the antagonist to the paralytic muscle stretched the elastic band and moved the eye. Relaxation of the antagonist muscle allowed the silicone band to move back to the resting position. In some cases, a weakening procedure of the antagonist muscle was also necessary. Rotations of up to 35 degrees in the field of action of the paralytic muscle were obtained within the first week after surgery, with a total amplitude of horizontal movement of up to 55 degrees. The best results seen six or more months after surgery were 18 degrees in the field of action of the paralytic muscle and 35 degrees of total amplitude of horizontal movement. This technique will require additional refinements, but this approach could prove to be an alternative procedure to reestablish ocular movement in cases where current techniques are not applicable.—Michael A. Kass

\*Department of Ophthalmology, School of Medicine of Fibeirão Preto, 14049 Ribeirão Preto, São Paulo, Brazil.

**The plain radiograph in ophthalmology: a wasteful and potentially dangerous anachronism.** Moseley, I. F.\*: *J. R. Soc. Med.* 84:76, 1991.

#### SKULL X-RAYS, ORBITAL AND INTRACRANIAL LESIONS

The indications for 822 consecutive referrals for skull X-rays were prospectively studied in a



large eye hospital over a one-year period. In 706 of 822 patients (85.9%), the results of the skull x-rays were normal, and in 103 of 116 of the remaining patients (89%), the results had no positive effect on management. All patients in whom a beneficial effect was identified would have been more appropriately investigated by other means, such as computed tomography scanning or magnetic resonance imaging. Fourteen of 25 patients whose skull

X-rays were normal were shown by computed tomography or magnetic resonance imaging to have orbital or intracranial lesions. With appropriate use of alternative imaging methods, no patient's treatment would have been adversely affected if skull X-rays had been deleted.—  
Michael A. Kass

\*Moorfields Eye Hospital, City Rd., London EC1, England.

Michael A. Kass, M.D., former associate editor and currently abstract editor of THE AMERICAN JOURNAL OF OPHTHALMOLOGY, was named editor-in-chief by the Board of Directors of the Ophthalmic Publishing Company at their meeting June 7, 1991. Dr. Kass is professor of ophthalmology at Washington University in St. Louis. He will succeed Frank W. Newell, M.D., Jan. 1, 1992.

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## NEWS ITEMS

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**Send News Items to**  
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### **Canadian Implant Association: Florida Winter Workshop**

The Canadian Implant Association will sponsor its annual Florida Winter Workshop, Dec. 27-29, 1991, at the Diplomat Resort Hotel in Hollywood, Florida. For further information, write Marvin L. Kwitko, M.D., Program Chairman, 5591 Cote des Neiges Rd., Montreal, Quebec, Canada H3T 1Y8; telephone (514) 735-1133.

### **German Ophthalmological Society: Update on Infectious Diseases of the Eye**

The German Ophthalmological Society will sponsor an International Symposium, Update on Infectious Diseases of the Eye, at Münster, Germany, Sept. 19-21, 1991. For further information, write CCM Cologne Congress Management GmbH, Schildergasse 101a, P.O. Box 180180, 5000 Cologne 1; fax 0221-249447.

### **American Society of Ophthalmic Registered Nurses: Annual Meeting**

The American Society of Ophthalmic Registered Nurses Annual Meeting will be Oct. 13-16, 1991, at Anaheim, California. For more information, write ASORN Headquarters, P.O. Box 3030, San Francisco, CA 94229; telephone (415) 561-8513.

### **Emory University School of Medicine and Medical College of Georgia: Pediatric Ophthalmology**

Emory University School of Medicine and the Medical College of Georgia will cosponsor a conference, Pediatric Ophthalmology, Sept. 20, 1991. For additional information, write Emory University School of Medicine, Continuing

Medical Education Dept., 1440 Clifton Rd., Atlanta, GA 30322; telephone (404) 727-5695.

### **Englewood Hospital: Recent Advances in the Diagnosis and Surgical Management of Lacrimal Disorders**

The Englewood Hospital will sponsor a conference, Recent Advances in the Diagnosis and Surgical Management of Lacrimal Disorders, Sept. 21, 1991, at the Englewood Hospital in Englewood, New Jersey. For more information, write Evelyn LeClair, Englewood Hospital, 350 Engle St., Englewood, NJ 07631; telephone (201) 894-3134.

### **Lexington Humana Hospital: Clinical Advances in Cataract, Glaucoma and Corneal Surgery**

Lexington Humana Hospital will sponsor two programs Sept. 20 and 21, 1991, in Lexington, Kentucky—Focus on the Future: 1991 Clinical Update for Ophthalmic Nurses and Technicians on Sept. 20 and Corneal-Contact Lens Update 1991 on Sept. 21. For more information, write Kay Montgomery, Lexington Humana Hospital, 150 N. Eagle Creek, Lexington, KY 40509; telephone (606) 268-3754.

### **New York University Department of Ophthalmology: Advances in Ocular Surgery**

New York University's Alumni Day program, Advances in Ocular Surgery, will be held Sept. 21, 1991, at the NYU Medical Center. For more information, write NYU Medical Center, Post-Graduate Medical School, 550 First Ave., New York, NY 10016; telephone (212) 263-5295.

### **St. Joseph Hospital, Baltimore: Diabetic Retinopathy—Review and Update**

The Retina Center at St. Joseph Hospital in Baltimore and the American Diabetes Association will sponsor a course, Diabetic Retinopathy, Sept. 20, 1991, in Baltimore, Maryland. For additional information, write Ruby Richardson, Conference Coordinator, The Retina Center, St. Joseph Hospital, P.O. Box 20,000, Baltimore, MD 21284; telephone (301) 337-4500.

### **St. Louis Ophthalmological Society: New Officers**

The St. Louis Ophthalmological Society elected the following officers at the annual



membership meeting on April 25, 1991: Robert D. Lewis, president; Allen F. Tess, vice president; and R. Joseph Olk, secretary-treasurer.

#### **New York Society for Clinical Ophthalmology: New Officers**

The New York Society for Clinical Ophthalmology elected the following officers for 1991-1992: Robert Rich, president; Frederick M. Wang, chairman, Program Committee; Stanley Chang, chairman, Membership Committee; Thomas O. Muldoon, treasurer; Dorothy N. Friedberg, correspondence secretary; Kevin C. Greenidge, historian; and Ronald M. Burde, recording secretary.

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#### **Personals**

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##### **John Clarkson**

John Clarkson, professor of ophthalmology at the University of Miami School of Medicine's Bascom Palmer Eye Institute, has been appointed chairman of the Department of Ophthalmology and medical director of the Institute. He succeeds Edward W. D. Norton.

##### **Carl Kupfer**

Carl Kupfer, director of the National Eye Institute, received the Distinguished Presidential Rank Award and a \$20,000 stipend from President George Bush. Dr. Kupfer was cited for his "sustained extraordinary accomplishment in management of programs of the United States Government and for leadership exemplifying the highest standards of service to the public, reflecting credit on the career civil service."

##### **Robert B. Nussenblatt**

Robert B. Nussenblatt will deliver the first Harvey B. Taterka lecture at the New York University Ophthalmology Alumni Day on Sept. 21, 1991. Dr. Nussenblatt, the clinical director of the National Eye Institute, will speak on the surgical management of uveitis. The lectureship commemorates the memory of Harvey B. Taterka, an important member of the department who was primarily involved in resident training at New York University from 1961 until his death in 1990.

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The Chicago Manual of Style, ed. 13. Chicago, University of Chicago Press, 1982.

Strunk W., Jr., and White, E. B.: The Elements of Style, ed. 3. New York, Macmillan Publishing Co., 1979.



# Ecosystem out of balance



**Compromised corneal endothelium**  
(SEM magnification 1000×)\*



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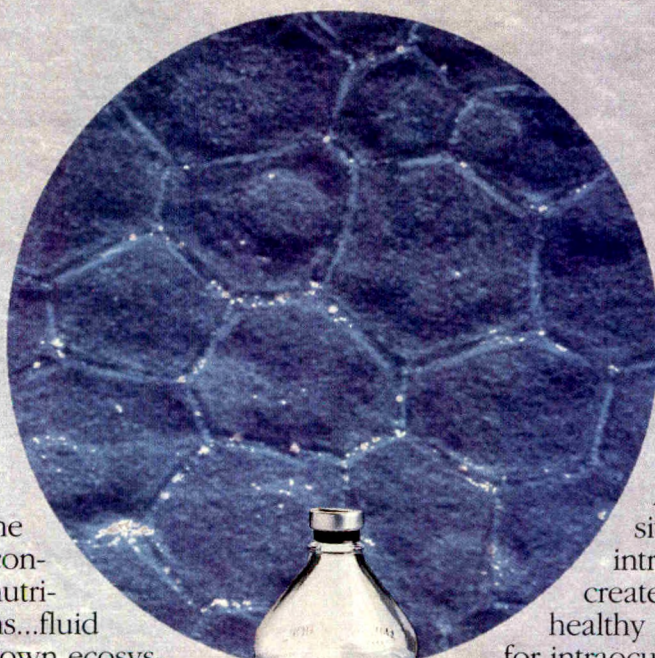
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# Keep the ecosystem intact



The eye, perhaps more than any other part of the body, comprises a self-contained environment of nutrients...pressure conditions...fluid exchanges...in short, its own ecosystem. The endothelial cells shown on the preceding page\* have been adversely affected by an out-of-balance ecosystem.

Only a complete, well-balanced perfusion medium can maintain the delicate fluid balance of the endothelium during intraocular irrigation.



And only the comprehensive formula of BSS PLUS® intraocular irrigating solution creates and maintains such a healthy endothelial environment for intraocular tissue survival (see SEM above\*).

Be kind to the environment. Call 1-800-TO ALCON for more information about how BSS PLUS® solution supplies the corneal endothelium with ecologically sound nourishment.

## BSS PLUS® Food for healthy post-op corneas

Sterile Intraocular Irrigating Solution

(Balanced Salt Solution Enriched with Bicarbonate, Dextrose, and Glutathione)

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SURGICAL

Innovation  
Without  
Compromise

\*Edelhauser HF. Intraocular irrigating solutions. In: Lamberts DW, Potter DE, eds. *Clinical Ophthalmic Pharmacology*. Boston, Mass: Little, Brown; 1987:431-444.

Pictured are SEM photos of human corneal cells following in vitro endothelial perfusion with BSS (preceding page) and BSS PLUS (above).

Please see brief summary of prescribing information on the next page.

Alcon Surgical, Inc., 6201 South Freeway, Fort Worth, TX 76134  
1-800-TO ALCON (1-800-862-5266)

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**BSS PLUS\***

(Balanced Salt Solution Enriched with  
Bicarbonate, Dextrose and Glutathione)  
Sterile Intraocular Irrigating Solution

**DESCRIPTION:** BSS PLUS\* is a sterile intraocular irrigating solution for use during all intraocular surgical procedures, even those requiring a relatively long intraocular perfusion time (e.g., pars plana vitrectomy, phacoemulsification, extracapsular cataract extraction/lens aspiration, anterior segment reconstruction, etc).

The solution does not contain a preservative and should be prepared just prior to use in surgery.

**Part I:** A sterile 480 mL solution in a 500 mL single-dose bottle to which the Part II concentrate is added. Each mL of Part I contains: Sodium Chloride 7.44 mg, Potassium Chloride 0.395 mg, Dibasic Sodium Phosphate 0.433 mg, Sodium Bicarbonate 2.19 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection. DM-00

**Part II:** A sterile concentrate in a 20 mL single-dose vial for addition to Part I. Each mL of Part II contains: Calcium Chloride Dihydrate 3.85 mg, Magnesium Chloride Hexahydrate 5 mg, Dextrose 23 mg, Glutathione Disulfide (Oxidized Glutathione) 4.6 mg, in Water for Injection. DM-00

After addition of BSS PLUS Part II to the Part I bottle, each mL of reconstituted product contains: Sodium Chloride 7.14 mg, Potassium Chloride 0.38 mg, Calcium Chloride Dihydrate 0.154 mg, Magnesium Chloride Hexahydrate 0.2 mg, Dibasic Sodium Phosphate 0.42 mg, Sodium Bicarbonate 2.1 mg, Dextrose 0.92 mg, Glutathione Disulfide (Oxidized Glutathione) 0.184 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection.

The reconstituted product has a pH of approximately 7.4. Osmolality is approximately 305 mOsm.

**CONTRAINDICATIONS:** There are no specific contraindications to the use of BSS PLUS, however, contraindications for the surgical procedure during which BSS PLUS is to be used should be strictly adhered to.

**WARNINGS:** For IRRIGATION during ophthalmic surgery only. BSS PLUS is NOT for injection or intravenous infusion.

**PRECAUTIONS:** DO NOT USE BSS PLUS UNTIL RECONSTITUTED. Do not use Part I if it does not contain a vacuum. Do not use additives other than Part II. Do not use if Part I, Part II or the reconstituted solution is discolored or contains a precipitate. SINCE BSS PLUS IS INTENDED FOR INTRAOCULAR IRRIGATION, IT DOES NOT CONTAIN A PRESERVATIVE AND, THEREFORE, SHOULD NOT BE USED FOR MORE THAN ONE PATIENT. DISCARD ANY UNUSED SOLUTION SIX HOURS AFTER PREPARATION. Studies suggest that intraocular irrigating solutions which are iso-osmotic with normal aqueous fluids should be used with caution in diabetic patients undergoing vitrectomy since intraoperative lens changes have been observed.

There have been reports of corneal clouding or edema following ocular surgery in which BSS PLUS was used as an irrigating solution. As in all surgical procedures, appropriate measures should be taken to minimize trauma to the cornea and other ocular tissues.

**ADVERSE REACTIONS:** Postoperative inflammatory reactions as well as incidents of corneal edema and corneal decompensation have been reported. Their relationship to the use of BSS PLUS has not been established.

**OVERDOSAGE:** The solution has no pharmacological action and thus has no potential for overdosage. However, as with any intraocular surgical procedure, the duration of intraocular manipulation should be kept to a minimum.

U.S. Patent Nos. 4,443,432 and 4,550,022

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Fort Worth, Texas 76134 USA

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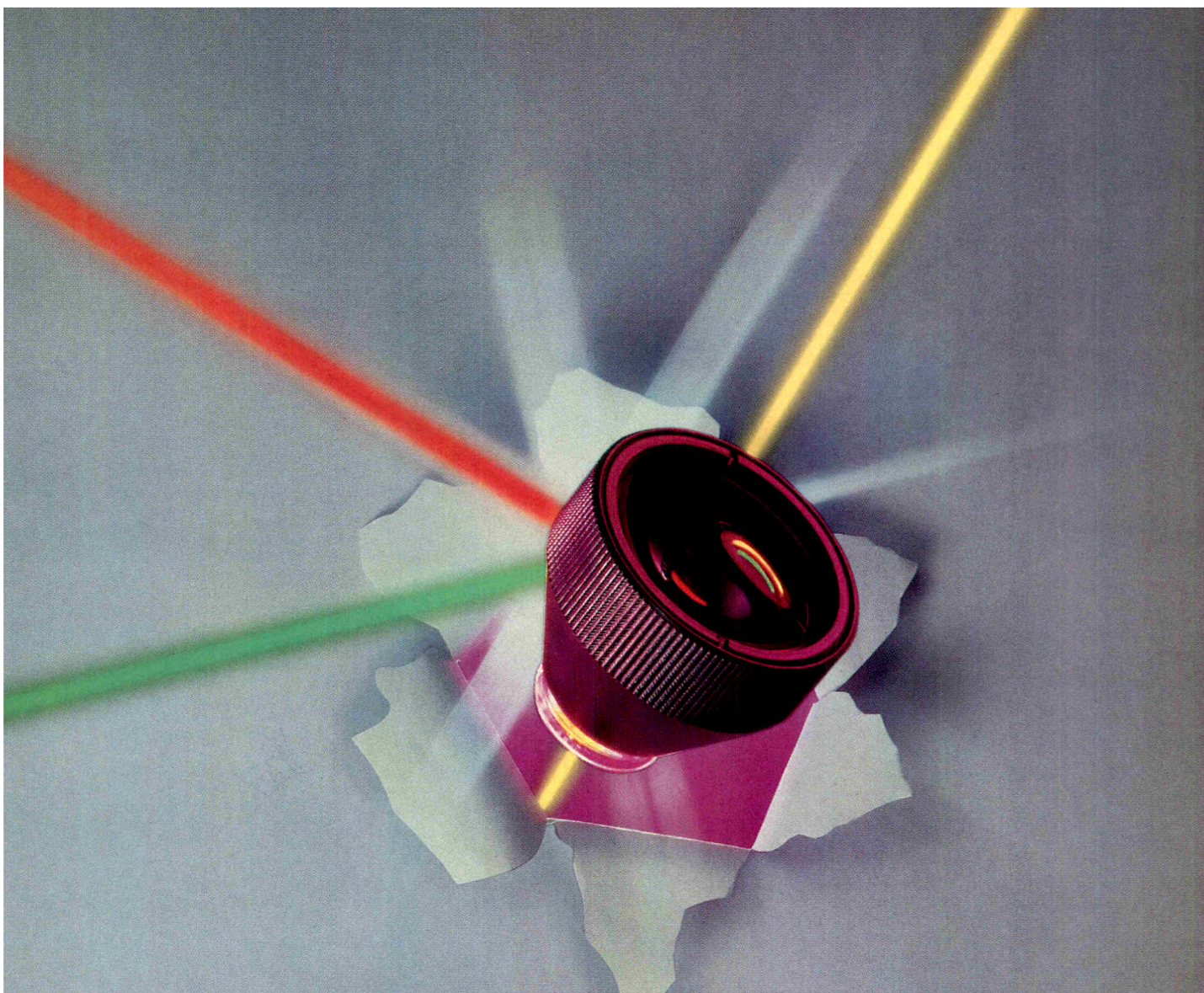
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For years, professionals have been sold on the Ocular Instruments Mainster Standard Retinal Laser Lens. Its higher magnification for grid or focal laser treatment permits detection of subtle intra-retinal details and retinal thickening, even through hazy ocular media and small pupils. For clarity, resolution, and viewing angle... these are clearly the lenses of choice for panretinal diagnosis and laser procedures.

To order and to request additional information, please contact: Ocular Instruments, Inc., 2255-116th Avenue NE, Bellevue, Washington 98004, (800) 888-6616.



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## PRODUCTS AND SERVICES

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### ► Contact Lens Supplies

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**Alcon Laboratories, Inc.**  
**6201 South Freeway**  
**Fort Worth, TX 76134-2099**  
**Tel: (800) 862-5266 (National)**  
**(817) 293-0450 (Texas)**

Alcon Laboratories, Inc. has introduced Opti-Free Enzymatic Cleaner for soft contact lenses. The weekly enzyme cleaner effectively removes all types of deposits from daily and extended wear soft contact lenses, and is gentle enough for sensitive eyes. Opti-Free Enzymatic Cleaner is also designed to promote lens care compliance by offering consumers easy, one-step enzyme cleaning and disinfection. Opti-Free enzyme tablets are pancreatin-based to avoid risk of papain or subtilisin sensitivity or irritation. Opti-Free Enzymatic Cleaner is effective in cleaning all three major types of lens deposits: protein, mucin, and lipid deposits. Because the cleaner is designed for use with Opti-Free Rinsing, Disinfecting & Storage Solution, lens wearers do not need a separate saline solution for weekly enzyme cleaning.

### ► Photographic Supplies

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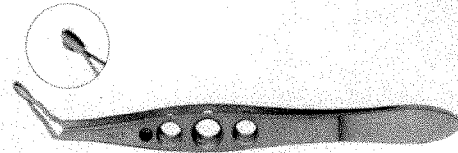
**Main Line Foto**  
**1100 East Hector Street**  
**Suite 120**  
**Conshohocken, PA 19428**  
**Tel: (800) 233-5204 (National)**  
**(215) 941-6424 (Pennsylvania)**  
**Fax: (215) 941-6430**

Main Line Foto, Inc., an authorized Kodak dealer and supplier of Fuji photographic films, has expanded its product line to include ophthalmic films. In consultation with ophthalmic photographers, Main Line Foto has developed a color coded packaging system for its ophthalmic films. In keeping with an established color reference system, retinal films, including Ektachrome and Fujichrome, will be packaged in red cassettes. Fluorescein films, including T-Max, Tri-X and HP-Plus, will be packaged in green cassettes. All cassettes will carry a write-on label that will enable the photographer to note patient name and identification information. These color coding and labeling systems are Main Line exclusives.

### ► Surgical Instruments

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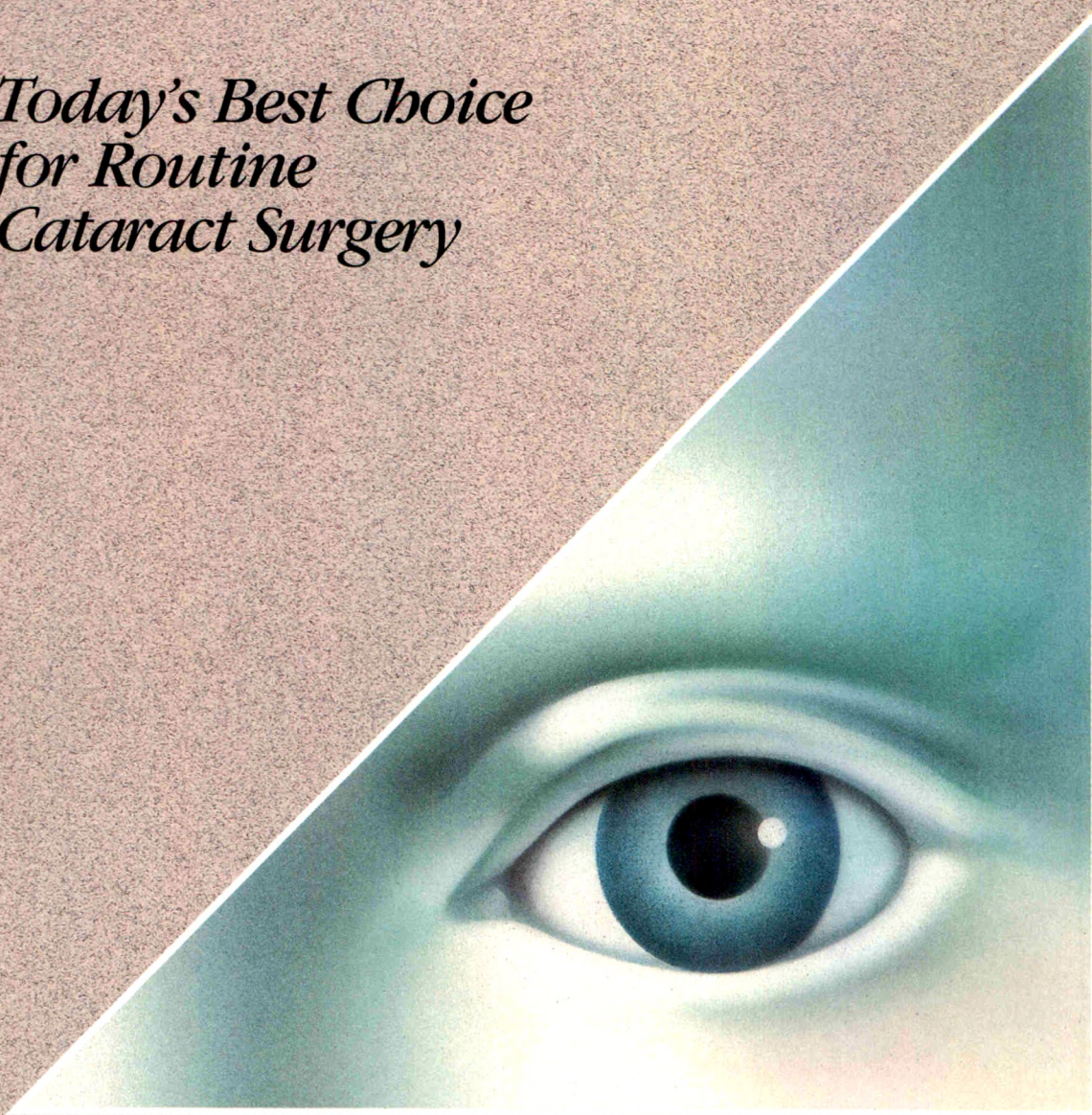
**Katena Products, Inc.**  
**4 Stewart Court**  
**Denville, NJ 07834**  
**Tel: (201) 989-1600**  
**Fax: (201) 989-8175**



Katena has introduced two new forceps with substantially smaller jaws for folding and inserting soft intraocular lenses. The very thin, curved jaws of these forceps wrap snugly around the folded intraocular lens without protruding beyond the edge of the lens, giving the appearance of being part of the lens itself. Designed by Henry H. McDonald, M.D., of Pasadena, California, the patented cross-action mechanism of these forceps is limited to a 3.5-mm spread within the incision. Two models are available. The standard version, K5-8235 for surgeons who make their incision at, or near the corneoscleral limbus, and the extended version, K5-8237, for those surgeons who place their incision further away from the corneoscleral limbus.



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for Routine  
Cataract Surgery*



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*Balances Performance with Economy*

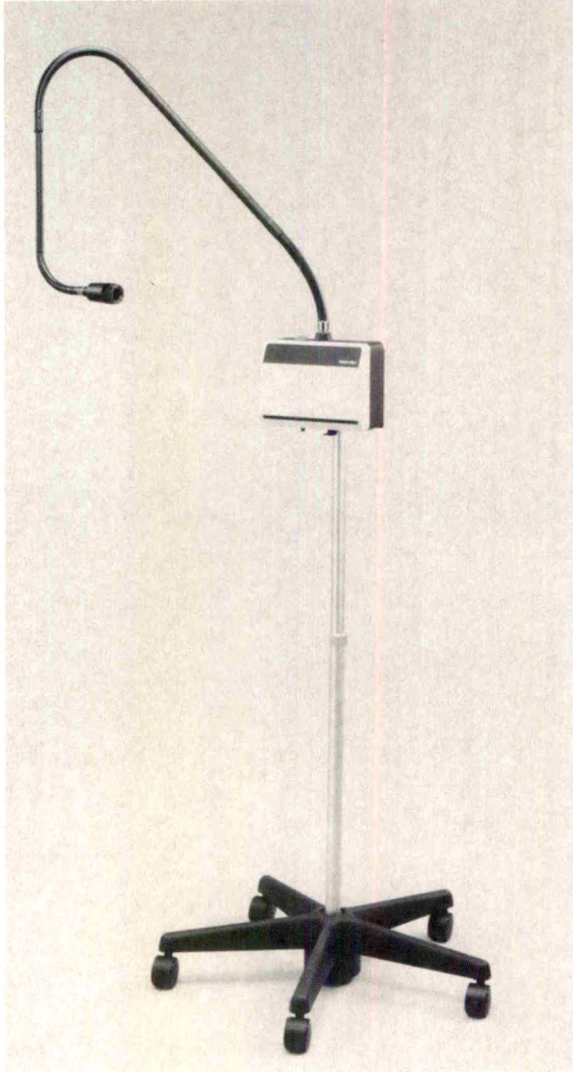


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## ► Diagnostic Devices

**Welch Allyn, Inc.**  
**Medical Division**  
**P.O. Box 220**  
**Skaneateles Falls, NY 13153-0220**  
**Tel: (315) 685-4560**



Welch Allyn, Inc., has introduced a new physician examination light for better visibility and more accurate diagnoses. Versatility and flexibility make the Exam Light II ideal for a full range of practices, including office-based, group practice, hospital, outpatient, freestanding clinic and surgicenter. A focusing sleeve provides a clear, homogeneous spot of light that is 65% larger. There is consistent illumination throughout the spot of light. The dichroic integral lamp reflector improves light output and allows for easier maintenance. A sturdy four-foot fiber optic light pipe transmits bright Halogen illumination without heat.

## ► Pharmaceuticals

**Optical Radiation Corporation**  
**1300 Optical Drive**  
**Azusa, CA 91702**  
**Tel: (800) 423-1887 (National)**  
**(800) 921-8754 (California)**  
**(818) 969-3344 (California)**

The Food and Drug Administration approved Orcolon, a high molecular weight viscoelastic manufactured by the Optical Radiation Corporation for use in intraocular surgical procedures. Orcolon is a highly purified polyacrylamide polymer that is supplied as a pyrogen-free sterile gel in a 0.75-ml disposable syringe. It does not require refrigeration. Three multicenter trials utilizing Orcolon (two in the United States and one in Canada) were conducted with patients who had undergone cataract surgery and intraocular lens implantation. Collectively, the results from all of these clinical studies demonstrate that Orcolon facilitates cataract removal and intraocular lens placement, maintenance of anterior chamber depth, and protection of ocular tissue. Numerous preclinical studies done with Orcolon (and the base polymerpolyacrylamide) indicate it is exceedingly safe. It is nonmutagenic, does not use lyse red blood cells, and is neither inhibitory nor toxic to mammalian cells in culture.

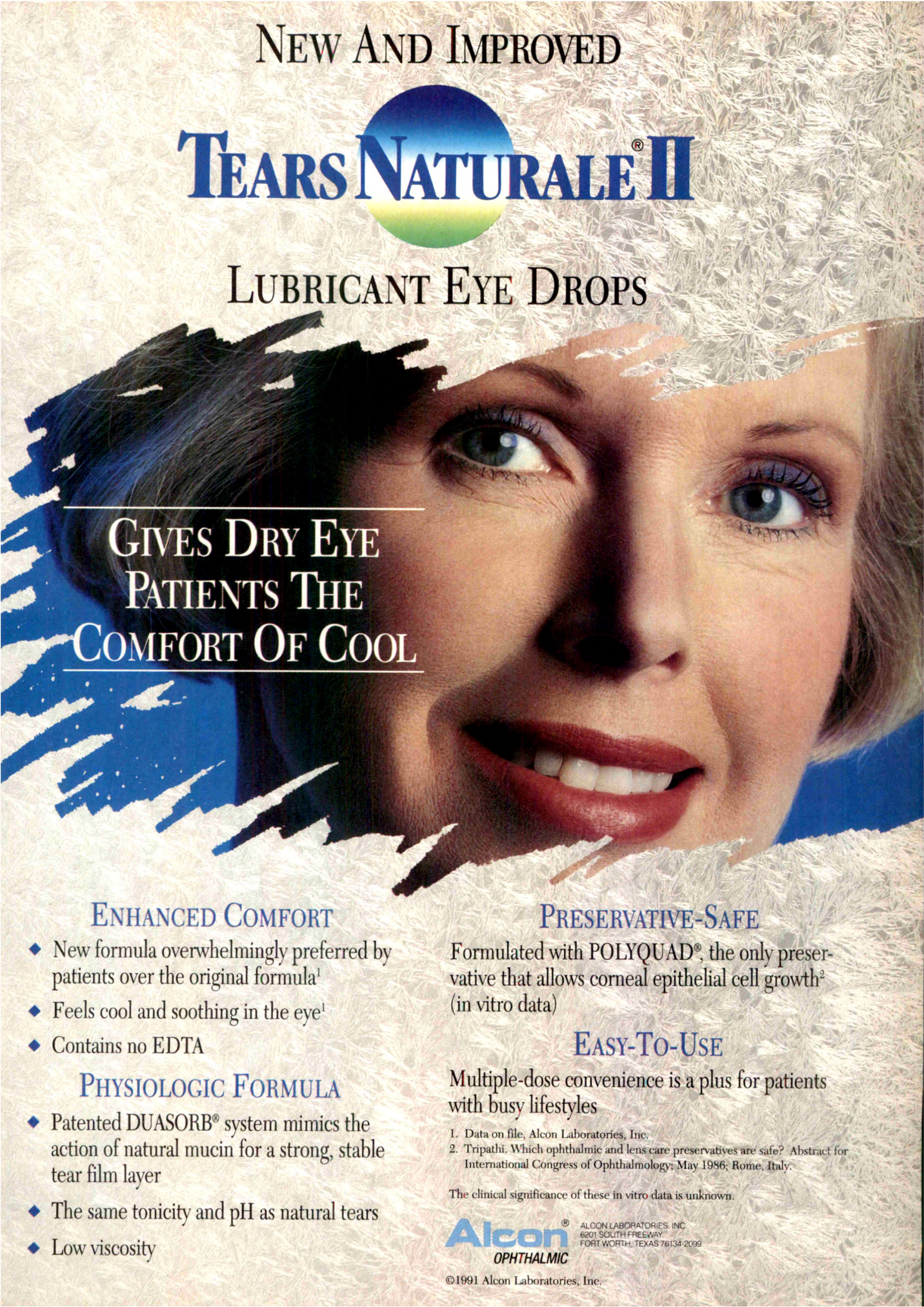
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**Dakryon Pharmaceuticals**  
**2579 South Loop 289, Suite 8**  
**Lubbock, TX 79423**  
**Tel: (800) 658-2024 (National)**  
**(806) 745-2872 (Texas)**  
**Fax: (806) 745-2549**

Dakryon Pharmaceuticals, a manufacturer of artificial tears, has begun operation in the new Center for Innovation of the Lubbock Board of City Development. Dakryon produces three eyedrops: NutraTear, Dakrina, and Dwelle. These products were formulated to relieve the problems of individuals who suffer from dry eyes. NutraTear, which contains vitamin B12, came on the market in 1989 for patients who have tired, irritated or red eyes. Dakrina and Dwelle were developed for patients who suffer from moderately to severe dry eyes. All three products are sold over the counter.



NEW AND IMPROVED



# TEARS NATURALE® II

## LUBRICANT EYE DROPS

GIVES DRY EYE  
PATIENTS THE  
COMFORT OF COOL

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- ◆ New formula overwhelmingly preferred by patients over the original formula<sup>1</sup>
- ◆ Feels cool and soothing in the eye<sup>1</sup>
- ◆ Contains no EDTA

### PHYSIOLOGIC FORMULA

- ◆ Patented DUASORB® system mimics the action of natural mucin for a strong, stable tear film layer
- ◆ The same tonicity and pH as natural tears
- ◆ Low viscosity

### PRESERVATIVE-SAFE

Formulated with POLYQUAD®, the only preservative that allows corneal epithelial cell growth<sup>2</sup> (in vitro data)

### EASY-TO-USE

Multiple-dose convenience is a plus for patients with busy lifestyles

1. Data on file, Alcon Laboratories, Inc.
2. Tripathi. Which ophthalmic and lens care preservatives are safe? Abstract for International Congress of Ophthalmology; May 1986; Rome, Italy.

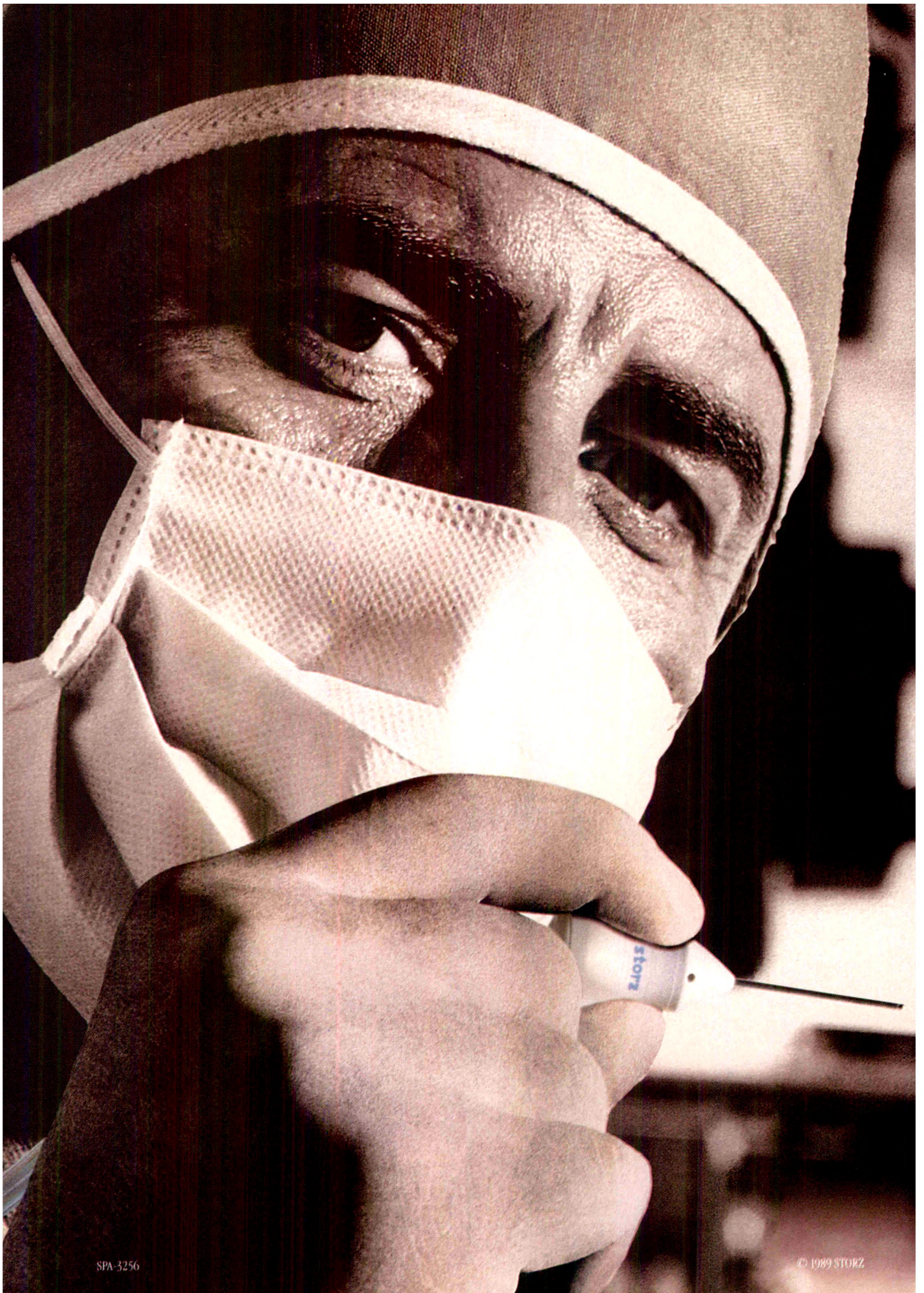
The clinical significance of these in vitro data is unknown.

**Alcon**  
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For posterior segment surgery, the new STORZ PREMIERE MICROVIT represents a significant advance in equipment reliability. With the remarkable vitreous cutting capability of the MICROVIT, and its new modular interior and multifunction footswitch, this system is a startling improvement over other systems for vitreoretinal surgery.

The PREMIERE MICROVIT. The one system to rely on for reliable posterior segment surgery.



The New STORZ PREMIERE™ MICROVIT®  
Because a reliable instrument is what you expect from STORZ.

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**DISPLAY ADVERTISING:** Display ads have a ruled border around the copy. Copy with more than 40 words will be considered a display ad. Each inch contains a maximum of 70 words.

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## POSITIONS AVAILABLE

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The Central New Jersey Medical Group, P.A., a multi-specialty group practice in association with HIP/Rutgers Health Plan, a federally qualified HMO in Central New Jersey is seeking a full-time board certified or board eligible ophthalmologist for the expansion of professional services. Excellent teaching hospitals, clinical academic appointments, membership in an active multi-specialty group practice. Liberal fringe benefits. Ideal location—close but not "too close" to the major metropolitan areas of NYC and Philadelphia. Send C.V.s to:

Dianne Nave, Physician Recruiter  
57 U.S. Highway #1  
New Brunswick, New Jersey 08901  
(908) 249-1246

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Well-established, ten member group of sub-specialists in Fort Worth, seeks board certified/board eligible associate to join busy, multi-site, high pathology practice. Generous benefits and salary plus bonus. Flexible work schedule. This is an unusually good opportunity. Send C.V. and photograph to Laura Cadahia, Ophthalmology Associates, 308 South Henderson, Fort Worth, Texas 76104.

**GENERAL OPHTHALMOLOGIST**—to join busy board certified ophthalmologist in Mid-Western U.S. resort area. New eye clinic and A.S.C. Responsibilities would include retina/vitreous, cataract, glaucoma, etc. Excellent salary plus incentives with possible partnership. Send C.V., photo and salary requirements to: BOX 3148, Spencer, IA 51301.

**RETINAL SPECIALIST:** Marshfield Clinic wishes to recruit a BC/BE retina specialist with a primary interest in medical retina. The prospective physician would be joining a medical and a surgical retina specialist plus cornea, glaucoma, pediatric, and neuro-ophthalmology specialists and three general ophthalmologists. The Marshfield Clinic is a 350+ physician multispecialty group practice serving Central and Northern Wisconsin as well as the Upper Peninsula of Michigan. Complete practice setup, support staff, and a full compliment of business office services are offered along with a competitive salary and excellent fringe benefits. This opportunity affords easy access to a wide variety of outdoor recreational activities, as well as safety and security for family living. For more information, send your C.V., or contact: Gary Pesicka, M.D., 1000 North Oak Avenue, Marshfield, WI 54449 or call (715) 387-5236.

**VITREORETINAL SURGEON:** Growing multi-doctor medical and surgical retina only referral practice desires an associate leading to partnership. Practice is well established with excellent facilities and equipment. Quality retinal fellowship required. Reply with C.V. to Box 222 AJO.

**VITREORETINAL SURGEON:** Prestigious, seven doctor, retina only, referral practice seeks associate leading to partnership. Private practice with academic affiliation. Send C.V. in confidence to Box 221 AJO.

**GENERAL OPHTHALMOLOGIST WANTED**—board eligible or board certified. Excellent opportunity to join a busy ophthalmology practice consisting of one main office and several satellite offices. Area served includes approximately 150,000 people. Located in Southeastern Pennsylvania approximately 1½ hours from Philadelphia, mostly semi-rural. This opportunity offers excellent salary and benefits with the potential of partnership. Send C.V. to: Fred L. Dankmyer, M.D., Box 220, Orwigsburg, PA 17961.

**TIRED OF TRAFFIC?** Earning too little? Board certified surgical ophthalmologist to join me in established 25 year private practice. Should be competent in retina. Inquiries to F. Thomas Ellingson, M.D., c/o Ellingson Eye & Laser Clinic, 626 N. 6th Street, Bismarck, North Dakota 58501. (Tel) 701-222-2020 (Fax) 701-255-7981.

### OCULOPLASTIC SURGERY UNIVERSITY OF MARYLAND MEDICAL CENTER

The Department of Ophthalmology is seeking a person who is fellowship trained in oculoplastic surgery to join us as an Assistant Professor. Clinical management of oculoplastics patients, expertise in oculoplastics orbit surgery, clinical research, and academic teaching are vital components of this position. Candidate must be BC/BE. An Affirmative Action/Equal Opportunity employer. Send C.V. by August 30, 1991 to:

Vinod Lakhanpal, M.D.  
Professor  
Department of Ophthalmology  
University of Maryland Medical Center  
22 S. Greene Street  
Baltimore, Maryland 21201

### NEURO-OPHTHALMOLOGIST UNIVERSITY OF MARYLAND MEDICAL CENTER

The Department of Ophthalmology is seeking a person who is fellowship trained in neuro-ophthalmology to join us as an Assistant Professor. Qualifications include a strong interest in teaching, research experience in clinical trials, and expertise in patient care. Candidate must be BC/BE in Ophthalmology or Neurology. An Affirmative Action/Equal Opportunity employer. Send C.V. or contact:

Shalom E. Keiman, M.D.  
Assistant Professor  
Department of Ophthalmology  
University of Maryland Medical Center  
22 S. Greene Street  
Baltimore, Maryland 21201  
(301) 328-7261

**GENERAL OPHTHALMOLOGIST:** Prestigious, well-established ophthalmology practice in Chicago and northern suburbs looking for associate to begin immediately. Fellowship training in plastics, medical retina or cornea is desirable but not mandatory. Potential for possible partnership. Salary negotiable. Reply to Box 223 AJO.

### OPHTHALMOLOGIST—IOWA

Iowa Ophthalmology Group seeking BC/BE Ophthalmologist interested in joining well established state-of-the-art practice with three BC/BE Ophthalmologists. Excellent opportunity to live in the midwest and enjoy family lifestyle. Send C.V. to Box 224 AJO.

**NEW JERSEY** multi-specialty group model HMO seeks well trained, ethical general ophthalmologist for its practice. Subspecialty interest helpful, but not essential. Competitive salary, benefits. EXCELLENT OPPORTUNITY FOR SUCCESSFUL CANDIDATE. Please send C.V., letter to Box 225 AJO.

### ACADEMIC OPHTHALMOLOGISTS Pediatric Ophthalmologist—Geneticist Retina and Vitreous Surgeon

The University of Nebraska College of Medicine, Department of Ophthalmology, is seeking two full-time academic ophthalmologists. A strong commitment to resident, medical student teaching, and research is essential. Requirements include completion of a satisfactory residency and American Board of Ophthalmology eligibility or certification. Must have documented prior teaching and research experience. Salary and rank commensurate with education and experience. Health Professions (tenure-leading) appointment contract with potential for renewal. Positions available immediately. Send C.V. to:

Michael E. Yablonski, M.D., Ph.D.  
Professor and Chairman  
Department of Ophthalmology  
University of Nebraska Medical Center  
600 South 42nd Street, Omaha, NE 68198-5540  
(402) 559-4276 FAX: (402) 559-5514  
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The Department of Ophthalmology, Harvard Medical School/Massachusetts Eye and Ear Infirmary, is recruiting a full-time retina faculty member at the level of Assistant or Associate Professor for the position of Medical Director of the Morse Laser Center. Requirements for this position include:

- 1) Completion of an approved eye residency program, appropriate fellowship training, and Board Certification;
- 2) Desire to provide specialty ophthalmic care;
- 3) Desire to participate in medical student, resident, and fellow education;
- 4) Demonstrated clinical practice management skills; and
- 5) Demonstrated track record in clinical research.

Interested persons should address all correspondence including a current C.V. to:

Frederick A. Jakobiec, M.D., Chairman  
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Massachusetts Eye and Ear Infirmary  
243 Charles Street, Boston, MA 02114  
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## VITREO-RETINAL FELLOWSHIP UNIVERSITY OF BRITISH COLUMBIA VANCOUVER, CANADA

**1 year, commencing July 1, 1992**

Fellowship to include extensive vitreous and retinal surgical experience, laser photocoagulation, fluorescein angiography, ultrasonography and clinical research projects.

*Send Curriculum Vitae to:*

A. L. Maberley, M.D., W. H. Ross, M.D.  
Department of Ophthalmology, U.B.C.  
2550 Willow Street  
Vancouver, B.C., Canada, V5Z 3N9  
(604) 875-4299

## FELLOWSHIPS

**NEURO-OPHTHALMOLOGY FELLOWSHIP:** Available for 1991-92, beginning 7/1/91. Salary and benefits paid. Qualified candidates should respond with current C.V. to B. K. Farris, M.D., Dean A. McGee Eye Institute, University of Oklahoma HSC, Department of Ophthalmology, P.O. Box 26901, Oklahoma City, Oklahoma 73190-2008.

**FELLOWSHIP:** Cornea/External Disease Fellowship available July 1, 1992. Clinical and animal research required. Excimer laser available. Contact: Richard A. Eiferman, M.D., University of Louisville, Department of Ophthalmology/Visual Sciences, Louisville, KY 40292.

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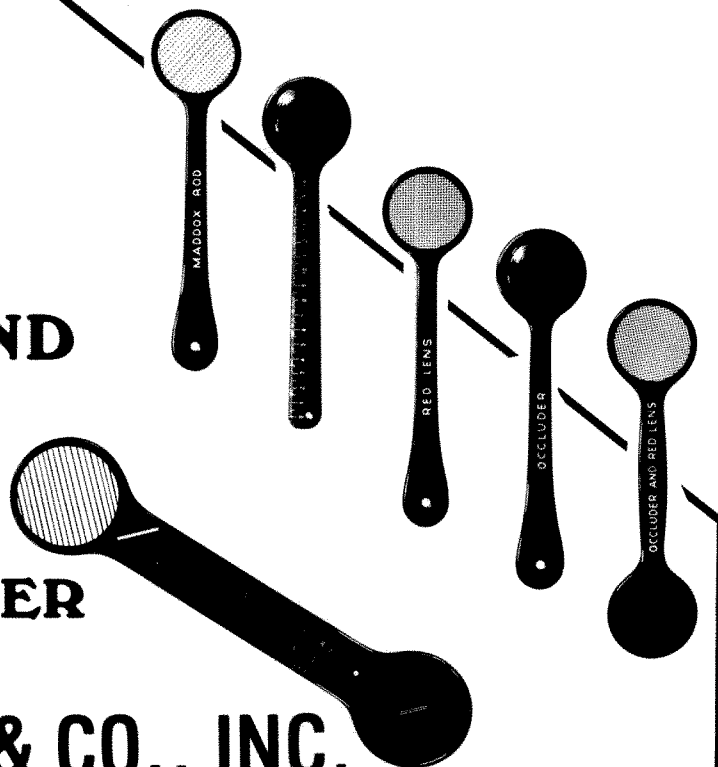
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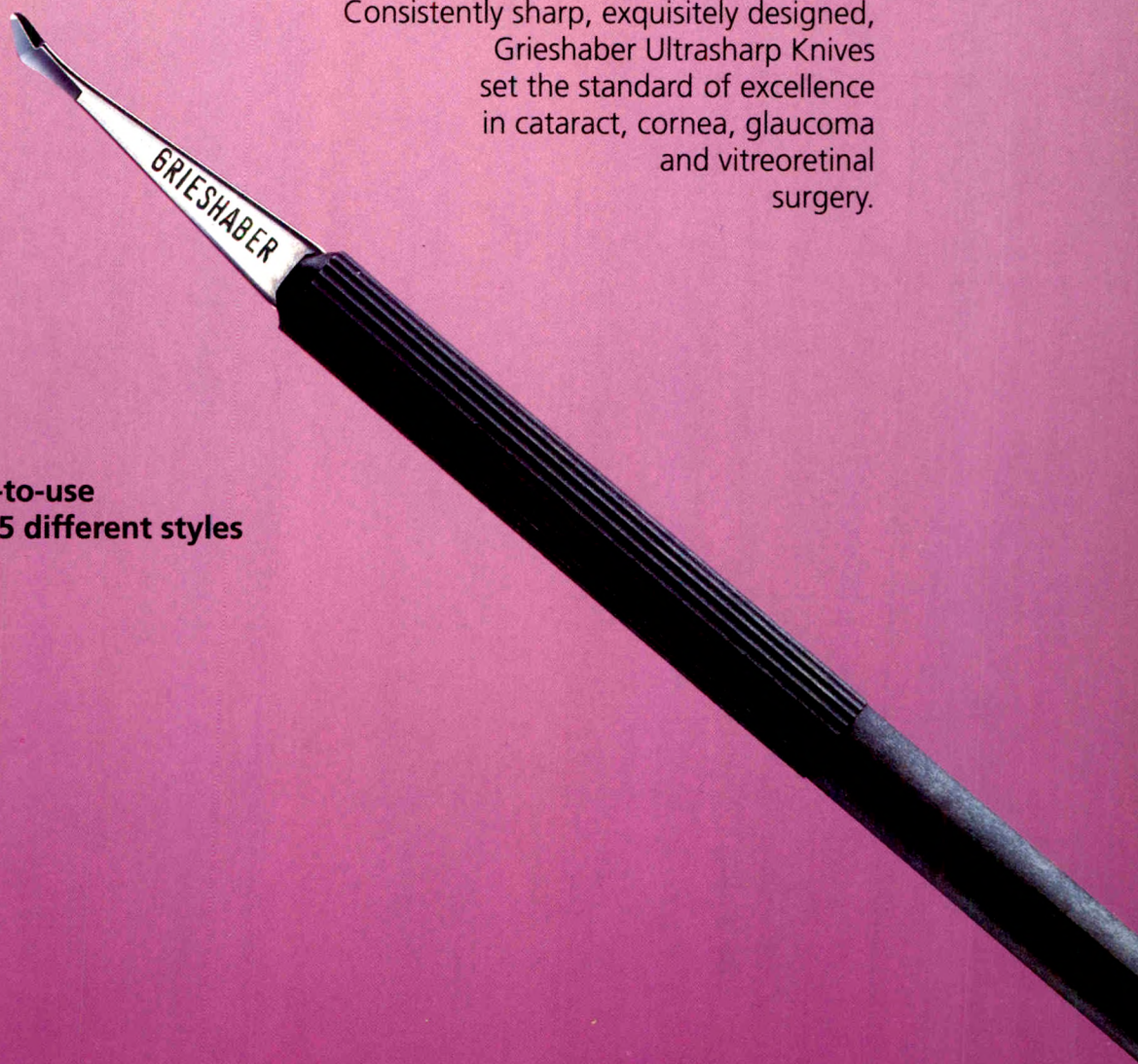
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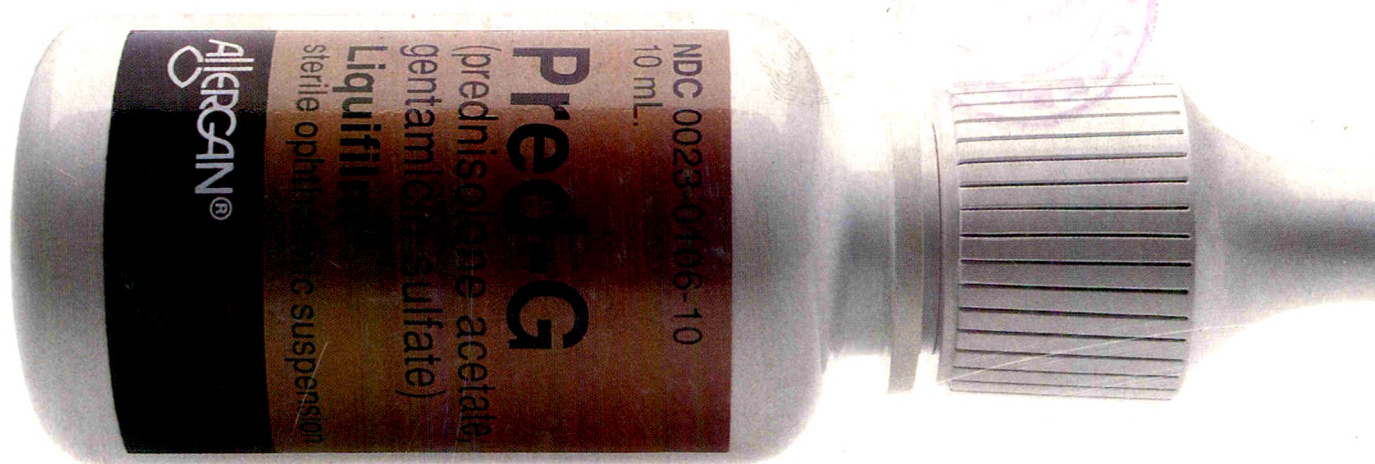
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**Vitreous Antibody Production in Uveitis**

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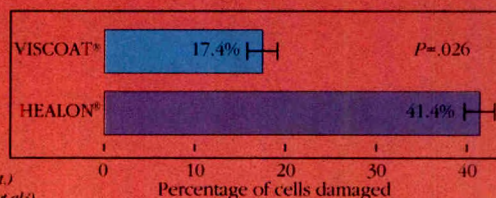
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#### References

1. Craig MT, Olson RJ, Mamalis N, Olson RJ. Air bubble endothelial damage during phacoemulsification in human eye bank eyes: The protective effects of Healon and Viscoat. *J Cataract Refract Surg.* 1990;16:597-602.

2. Glasser DB, Katz HR, Boyd JE, Langdon JD, Shobe SL, Peiffer RL. Protective effects of viscous solutions in phacoemulsification and traumatic lens implantation. *Arch Ophthalmol.* 1989;107:1047-1051.

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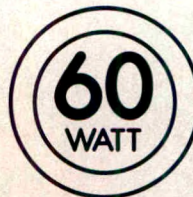
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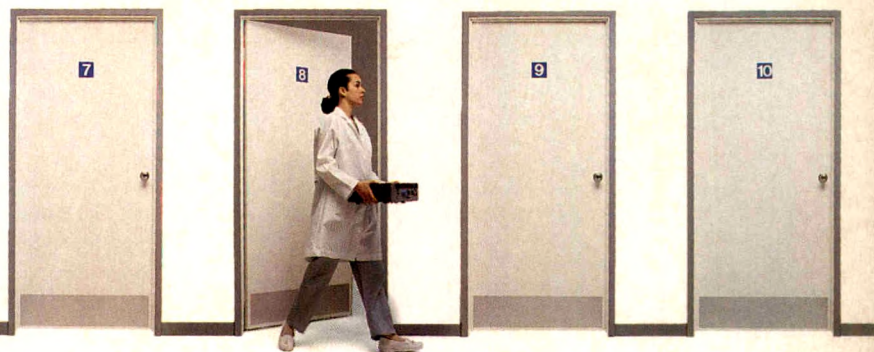
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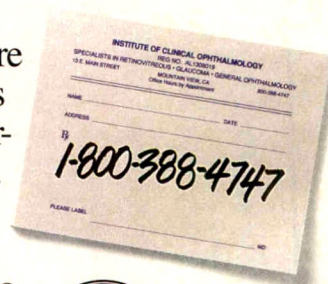
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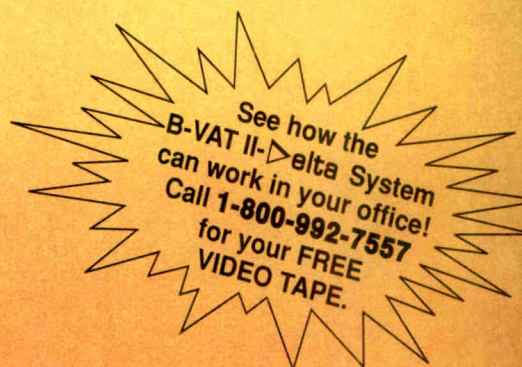
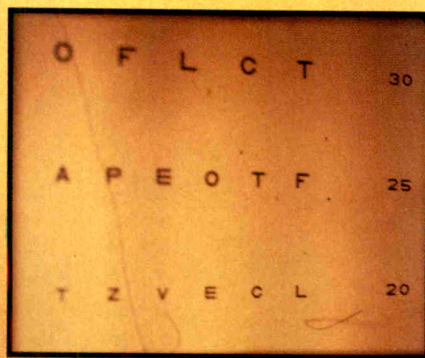


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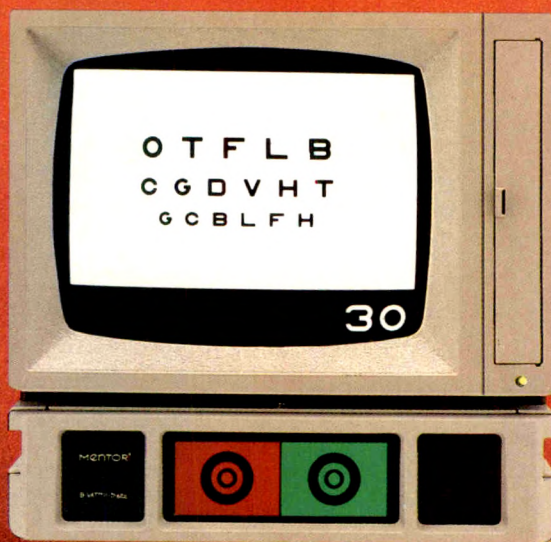
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
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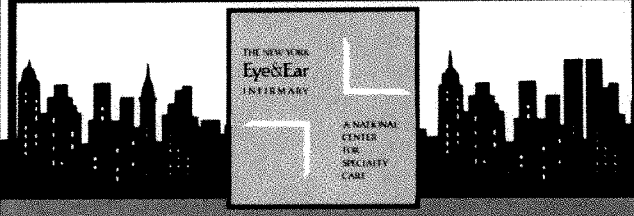
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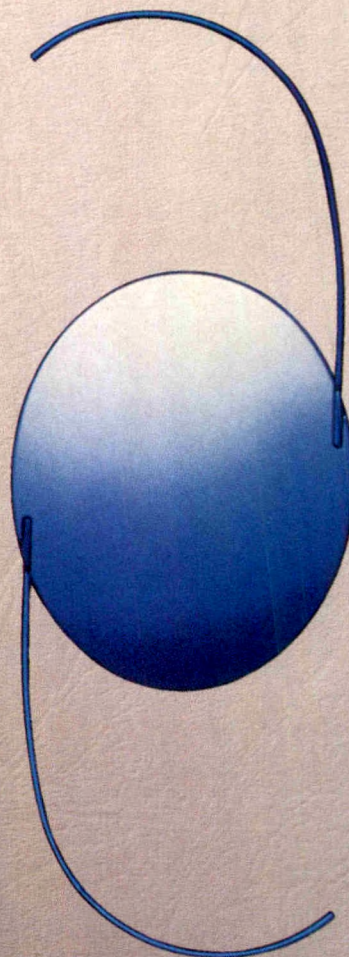
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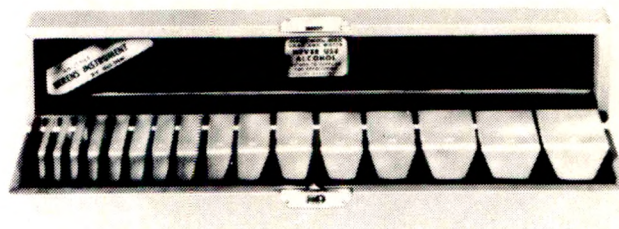
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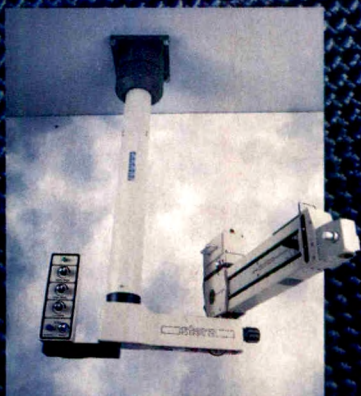
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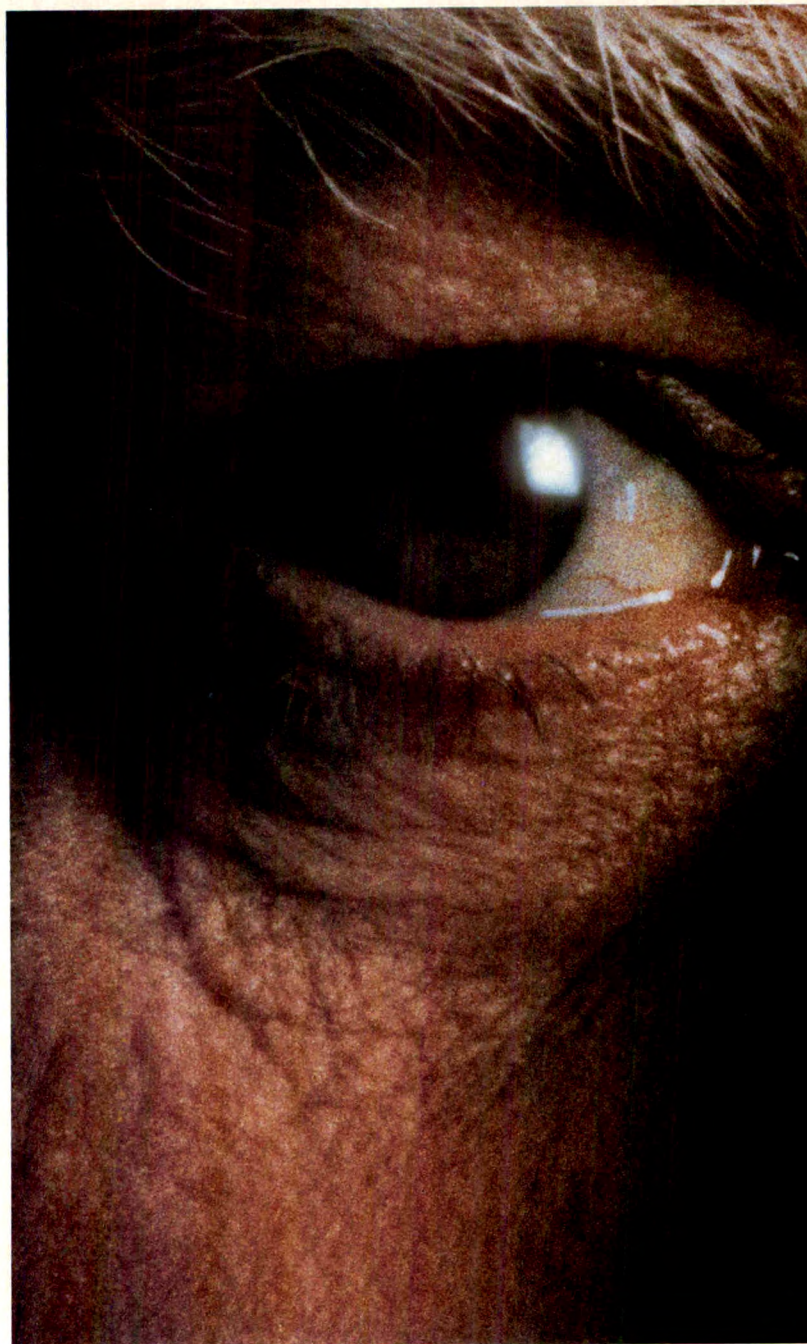
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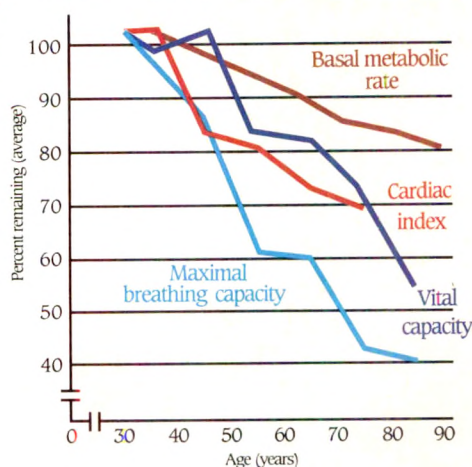
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#### References:

1. Givens KT, Lee DA. Topical beta blockers for glaucoma: what clinicians should know. *Geriatric Medicine Today*. 1989;8:105-113.
2. Feigenbaum LZ. Geriatric medicine and the elderly patient. In: Schroeder SA, Krupp MA, Tierney LM, eds. *Current Medical Diagnosis and Treatment 1988*. Norwalk, Conn: Appleton & Lange; 1988:17-26.
3. Conrad KA, Bressler R. Drugs and advanced age. In: Modell W, ed. *Drugs of Choice, 1984-1985*. St Louis, Mo: CV Mosby Co; 1984:21-40.
4. Data on file, Alcon Laboratories, Inc.
5. Schoene RB, et al. Effects of topical betaxolol, timolol and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol*. 1984;97:86-92.
6. Atkins JM, et al. Cardiovascular effects of topical beta blockers during exercise. *Am J Ophthalmol*. 1985;99:173-175.

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**WARNING:** Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents. BETOPTIC S Ophthalmic Suspension 0.25% has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S Ophthalmic Suspension 0.25% should be discontinued at the first signs of cardiac failure.

**PRECAUTIONS: General: Diabetes Mellitus.** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrotoxicosis.** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

**Muscle Weakness.** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

**Major Surgery.** Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. **Pulmonary.** Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. **Drug Interactions:** Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. **Pregnancy: Pregnancy Category C.** Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS: Ocular:** In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, edema and anisocoria. **Systemic:** Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include: **Cardiovascular:** Bradycardia, heart block and congestive failure. **Pulmonary:** Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure. **Central Nervous System:** Insomnia, dizziness, vertigo, headaches, depression, and lethargy. **Other:** Hives, toxic epidermal necrolysis, hair loss, and glossitis.

**OVERDOSAGE:** No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. A topical overdose of BETOPTIC S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

**CAUTION: Federal (USA) Law Prohibits Dispensing Without a Prescription.**  
U.S. Patent Nos. 4,252,984; 4,311,708; 4,342,783; 4,911,920.

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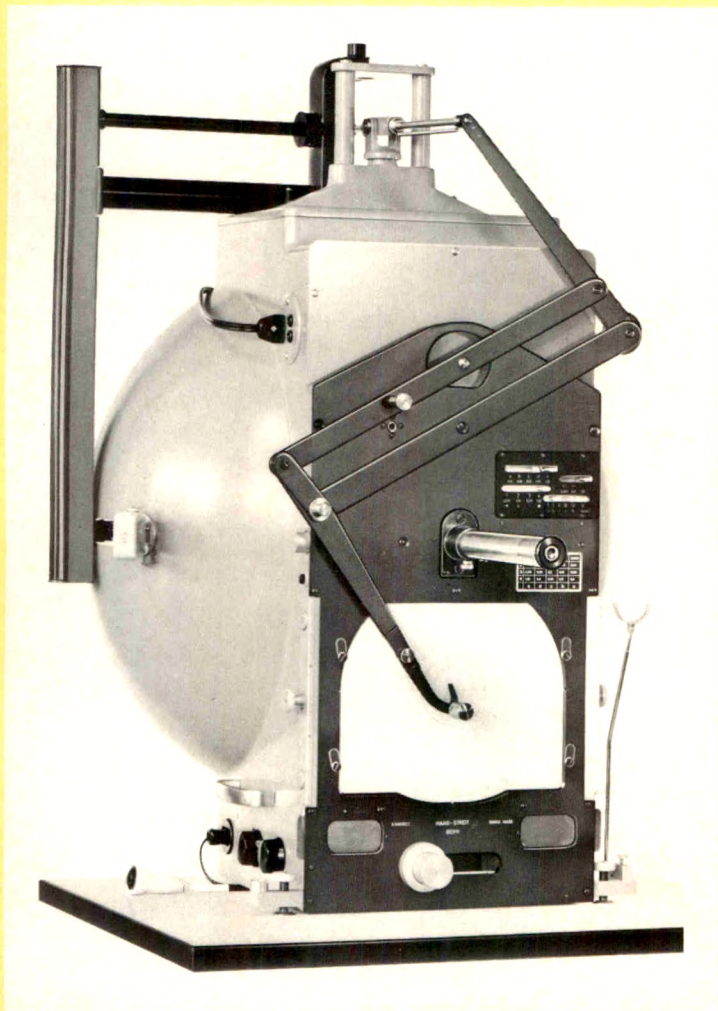
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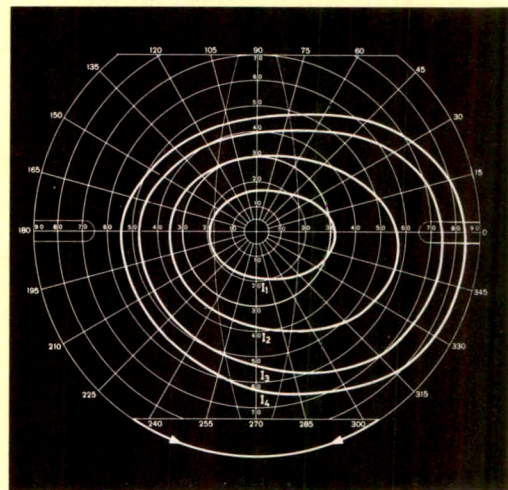
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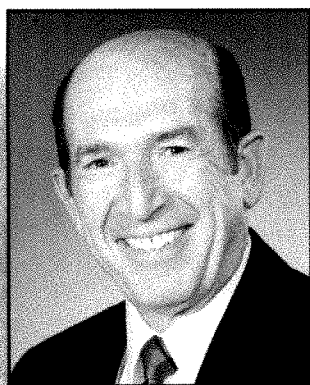
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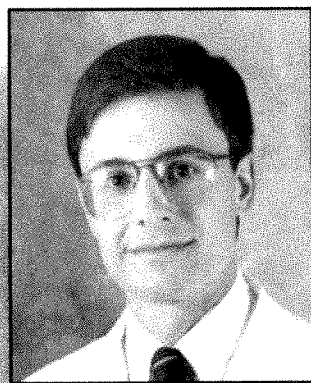
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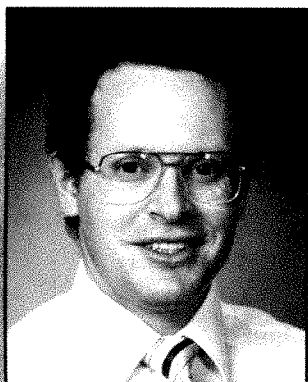
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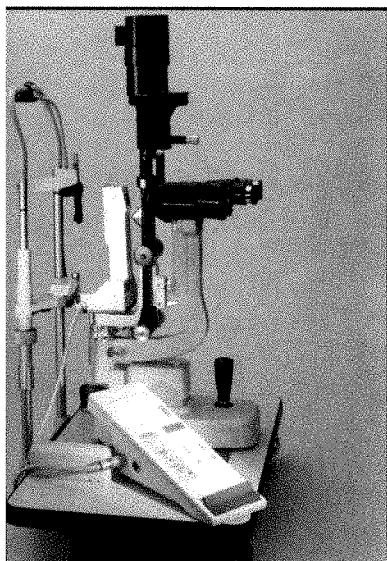
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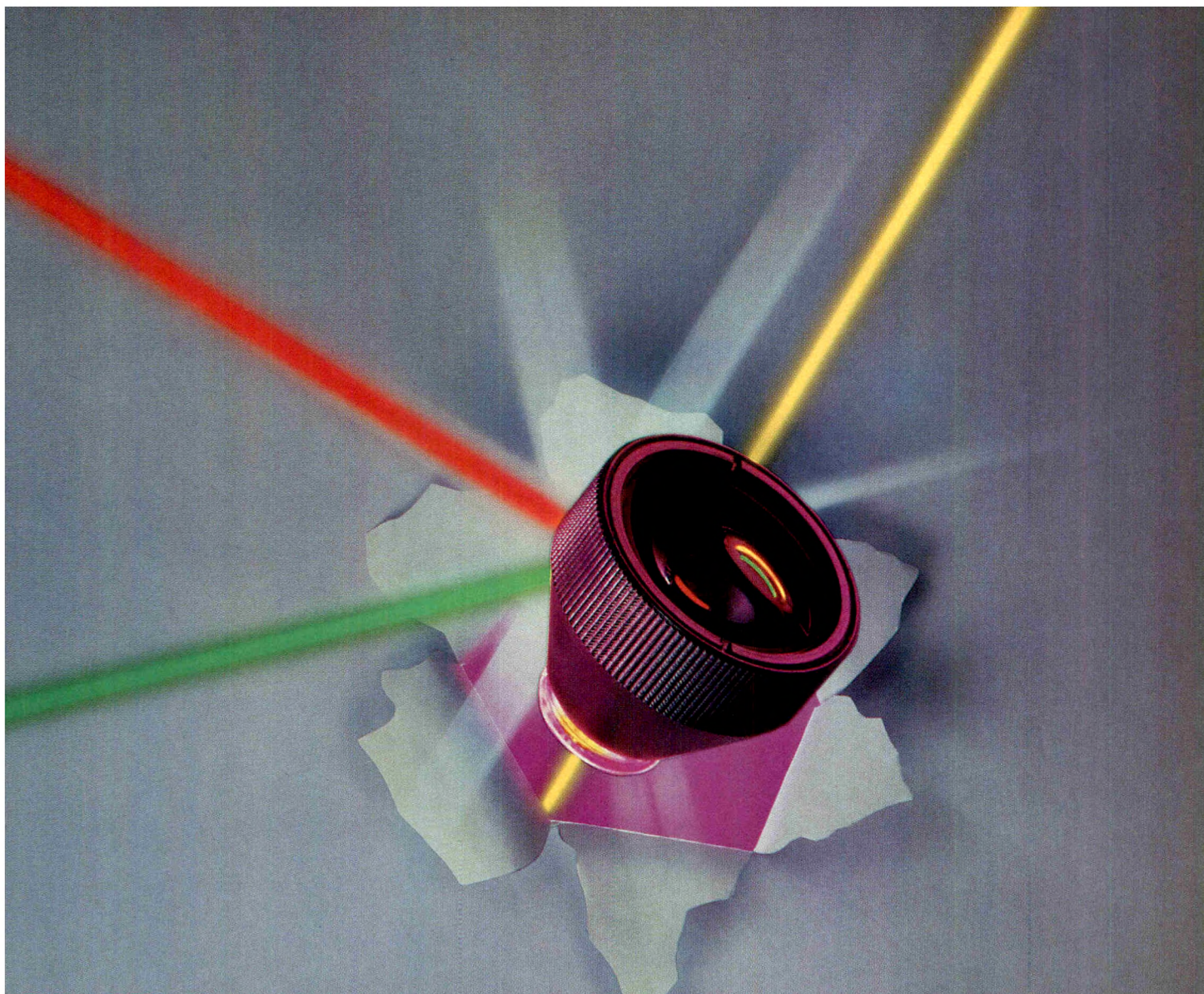
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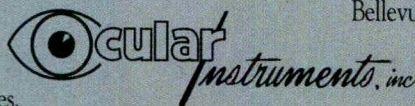
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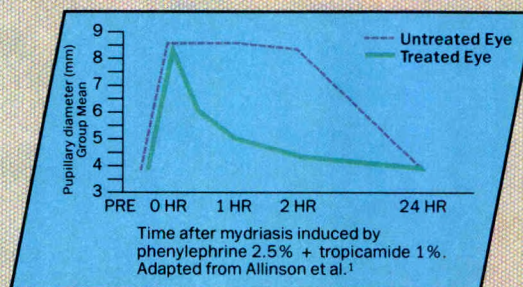


# An agent to reverse the diagnostic mydriasis induced by phenylephrine and tropicamide

**Significantly reduces the time your patients must wait for restoration of premydriatic pupillary diameter**

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**Increases patient convenience**

- Reduces blurry vision and glare while partially increasing accommodative amplitude. Patients may experience difficulty in dark adaptation; exercise caution while driving and in poor illumination.

## **Dosage**

2 drops into each eye followed 5 minutes later by 2 additional drops in each eye. Dapiprazole should not be used in the same patient more frequently than once per week.

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1. Allinson RW, Gerber DS, Bieber S, Hodes BL. Reversal of mydriasis by dapiprazole. *Ann Ophthalmol.* 1990;22:131-138.
2. Data on file, Storz Ophthalmics, St. Louis, Mo.

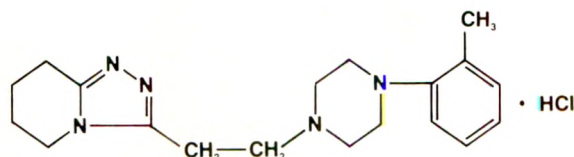
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**dapiprazole hydrochloride**  
**Ophthalmic Eyedrops, 0.5%—Sterile**

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RĒV-EYES is an alpha-adrenergic blocking agent.

Dapiprazole hydrochloride is 5,6,7,8-tetrahydro-3-[2-(4-o-tolyl-1-piperazinyl)ethyl]-s-triazolo[4,3-a] pyridine hydrochloride.



Dapiprazole hydrochloride has the empirical formula C<sub>19</sub>H<sub>27</sub>N<sub>5</sub> HCl and a molecular weight of 361.93.

Dapiprazole hydrochloride is a sterile, white, lyophilized powder soluble in water.

RĒV-EYES Eyedrops is a clear, colorless, slightly viscous solution for topical application. Each mL (when reconstituted as directed) contains 5 mg of dapiprazole hydrochloride as the active ingredient.

The reconstituted solution has a pH of approximately 6.6 and an osmolality of approximately 415 mOsm.

The inactive ingredients include: Mannitol (2%), Sodium Chloride, Hydroxypropyl Methylcellulose (0.4%), Edetate Sodium (0.01%), Sodium Phosphate Dibasic, Sodium Phosphate Monobasic, Water for Injection, and Benzalkonium Chloride (0.01%) as a preservative.

RĒV-EYES Eyedrops, 0.5% is supplied in a kit consisting of one vial of dapiprazole hydrochloride (25 mg), one vial of diluent (5 mL) and one dropper for dispensing.

### CLINICAL PHARMACOLOGY

Dapiprazole acts through blocking the alpha-adrenergic receptors in smooth muscle. Dapiprazole produces miosis through an effect on the dilator muscle of the iris.

Dapiprazole does not have any significant activity on ciliary muscle contraction and therefore does not induce a significant change in the anterior chamber depth or the thickness of the lens.

Dapiprazole has demonstrated safe and rapid reversal of mydriasis produced by phenylephrine and to a lesser degree tropicamide. In patients with decreased accommodative amplitude due to treatment with tropicamide the miotic effect of dapiprazole may partially increase the accommodative amplitude.

Eye color affects the rate of pupillary constriction. In individuals with brown irides, the rate of pupillary constriction may be slightly slower than in individuals with blue or green irides. Eye color does not appear to affect the final pupil size.

Dapiprazole does not significantly alter intraocular pressure in normotensive or in eyes with elevated intraocular pressure.

### INDICATIONS AND USAGE

Dapiprazole is indicated in the treatment of iatrogenically induced mydriasis produced by adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents. Dapiprazole is not indicated for the reduction of intraocular pressure or in the treatment of open angle glaucoma.

### CONTRAINDICATIONS

Miotics are contraindicated where constriction is undesirable; such as acute iritis, and in those subjects showing hypersensitivity to any component of this preparation.

### WARNING

For Topical Ophthalmic Use Only. NOT FOR INJECTION. Do not touch the dropper up to lids or any surface, as this may contaminate the solution. Dapiprazole should not be used in the same patient frequently than once a week.

### PRECAUTIONS

**Information to patients:** Miosis may cause difficulty in driving and may reduce the field of vision. Patients should exercise caution when involved in night driving or other activities in poor illumination. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Dapiprazole has been shown to significantly increase the incidence of liver tumors in rats after continuous dietary administration for 104 weeks. No effect was found only in male rats treated with the highest dose administered in the study, i.e., 300 mg/kg/day, (80,000 times the human dose) and was not observed in male and female rats at doses of 100 mg/kg/day and female rats at doses of 300 mg/kg/day.

Negative results have been reported on the mutagenicity and impairment of fertility studies with dapiprazole.

**Pregnancy:** Pregnancy Category B: Reproduction studies performed in rats and rabbits at doses up to 128,000 (rat) and 12,800 (rabbit) times the human ophthalmic dose and revealed no evidence of impaired fertility or harm to the fetus due to dapiprazole. However, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, nursing should be exercised when dapiprazole is administered to women.

**Pediatric use:** Safety and effectiveness in children has not been established.

### ADVERSE REACTIONS

In controlled studies the most frequent reaction to dapiprazole conjunctival injection lasting 20 minutes in over 80% of patients. On instillation of dapiprazole was reported in approximately 10% to 40% of patients. Reactions occurring in 10% to 40% of patients included ptosis, lid erythema, lid edema, chemosis, itching, punctate corneal edema, browache, photophobia and headaches. Concomitant reactions reported less frequently included dryness of eyes, tearing, and blurring of vision.

### DOSAGE AND ADMINISTRATION

Two drops followed 5 minutes later by an additional 2 drops topically to the conjunctiva of each eye should be administered. The ophthalmic examination to reverse the diagnostic mydriasis. Dapiprazole should not be used in the same patient more than once per week.

### Directions for Preparing Eyedrops:

1. Use aseptic technique.
2. Tear off aluminum seals, remove and discard rubber plugs from drug and diluent vials.
3. Pour diluent into drug vial.
4. Remove dropper assembly from its sterile wrapping and use the drug vial.
5. Shake container for several minutes to ensure mixing.

**Storage and Stability of Eyedrops:** Once the eyedrops have been reconstituted they may be stored at room temperature (59°-86°F) for 21 days. Discard any solution that is not colorless.

### HOW SUPPLIED

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Each package contains RĒV-EYES™ (25 mg), diluent (5 mL) per for dispensing.

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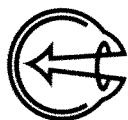
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**INDICATIONS AND USAGE:** Pred-G suspension is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies. The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye. The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: coagulase-positive and coagulase-negative staphylococci, including *Staphylococcus aureus*, and certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci, and *Streptococcus pneumoniae*; *Escherichia coli*; *Hemophilus influenzae*; *Klebsiella/Enterobacter* species; *Neisseria* species, including *Neisseria gonorrhoeae*; *Pseudomonas aeruginosa*; indole-positive and indole-negative *Proteus* species; and *Serratia marcescens*.

**CONTRAINDICATIONS:** Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of the ocular structures. Hypersensitivity to a component of the medication. (Hypersensitivity to the antibiotic component occurs at a higher rate than for other components.) Pred-G suspension is always contraindicated after uncomplicated removal of a corneal foreign body. **WARNINGS:** Prolonged use may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Employment of a steroid medication in the treatment of patients with a history of herpes simplex requires great caution. Pred-G suspension is contraindicated in patients with active herpes simplex keratitis. Pred-G Liquifilm sterile ophthalmic suspension is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye. **PRECAUTIONS:** The initial prescription and renewal of the medication order beyond 20 milliliters should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. The possibility of fungal infections of the cornea should be considered after prolonged steroid dosing.

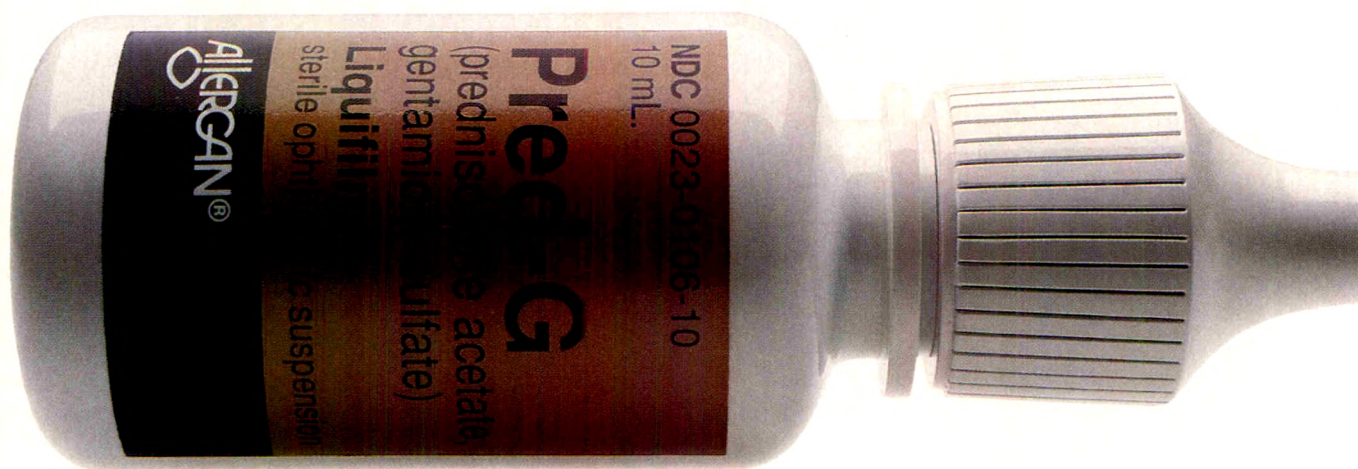
**ADVERSE REACTIONS:** Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available. Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitizations. The reactions due to the steroid component in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing. Burning, stinging and other symptoms of irritation have been reported with Pred-G. Superficial punctate keratitis has been reported occasionally with onset occurring typically after several days of use. **Secondary Infection:** The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.



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Employment of a steroid medication in the treatment of patients with a history of herpes simplex requires great caution. Pred-G is contraindicated in patients with active herpes simplex keratitis. See adjacent page for brief prescribing information.

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# Varicella-Zoster Virus Retinitis in Patients With the Acquired Immunodeficiency Syndrome

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We examined five patients infected with the human immunodeficiency virus who developed a rapidly progressive necrotizing retinitis characterized by early patchy choroidal and deep retinal lesions and late diffuse thickening of the retina. In all but one case, the retinitis began in the posterior pole with little or no clinical evidence of vasculitis. All five patients had relentless progression of disease and were left with atrophic and necrotic retinæ, pale optic-nerve heads, and narrowed vasculature. None of the patients developed aqueous or vitreal inflammation or retinal detachment. Clinical and laboratory evidence suggested that varicella-zoster virus was the causal agent in all five cases. First, the onset of retinitis in four cases either succeeded or was coincident with an eruption of dermatomal zoster. Second, varicella-zoster virus was cultured from the two chorioretinal specimens and varicella-zoster virus antigen was detected in the vitreal aspirate from one case. Third, by means of immunocytochemistry, varicella-

zoster virus antigen was found in the outer retinæ of both enucleation specimens. Fourth, viral capsids with the size and shape of herpesviridae were found in the outer retinæ of both enucleation specimens. The clinical features observed in this study are distinct from those described for the acute retinal necrosis syndrome and appear to constitute a new and highly characteristic pattern of varicella-zoster virus-induced disease.

FORSTER AND ASSOCIATES<sup>1</sup> recently described two cases of rapidly progressive retinal necrosis that were temporally related to episodes of zoster dermatitis in patients with the acquired immunodeficiency syndrome. They suggested that varicella-zoster virus was the cause of this syndrome, but were unable to culture virus from the retinal biopsy specimens obtained from either patient. We examined five patients infected with HIV who developed a rapidly progressive necrotizing retinopathy similar to that described by Forster and associates, and distinct from the more common necrotizing infection of the retina caused by cytomegalovirus. Clinical and laboratory study of our cases suggests that this new syndrome is caused by varicella-zoster virus.

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## Case Reports

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### Case 1

A 49-year-old man with AIDS developed acute bilateral visual loss. He was seropositive for HIV for three years and had previous episodes of *Pneumocystis carinii* pneumonia, severe aphthous ulcers, and systemic infection with *Mycobacterium avium* complex. At initial examination, he had bilateral multifocal choroidal and deep retinal inflammation, most

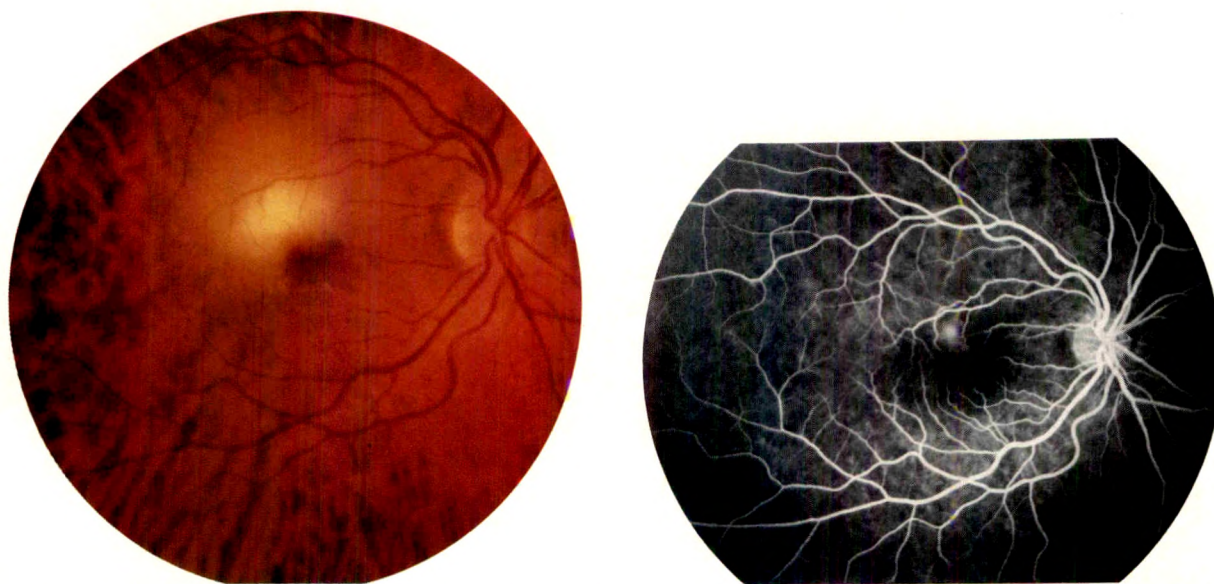
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**Fig. 1** (Margolis and associates). Case 1, right eye. Left, Fundus photograph showing intense focal retinitis superior to fovea at initial examination. Right, Full venous-phase fluorescein angiogram demonstrates intact vasculature and intraretinal staining corresponding to the area of retinitis.

prominently in the macula (Fig. 1, left). Vitreitis and iridocyclitis were absent. Fluorescein angiography disclosed multiple regions of extravascular leakage of dye corresponding with the areas of retinal whitening (Fig. 1, right). Vascular filling times were clinically normal. A diagnosis of multifocal choroiditis of unknown cause was considered.

After a one-week delay, empiric treatment with four days of intravenous administration of acyclovir was started. Laboratory evaluation at this time included a negative serum and cerebrospinal fluid VDRL test, and negative antibody titers to *Toxoplasma gondii*. The retinitis progressed and the patient was referred for further examination. The visual acuity at this time was 20/400 bilaterally. Patchy, choroidal and deep retinal lesions were observed bilaterally (Fig. 2, top). There was little or no vitreal reaction overlying the involved areas of retina. The maculae of both eyes were surrounded by thickened retinal tissue, giving them the appearance of a cherry-red spot. The optic nerve heads appeared clinically normal. The cause remained unclear and no further treatment was administered.

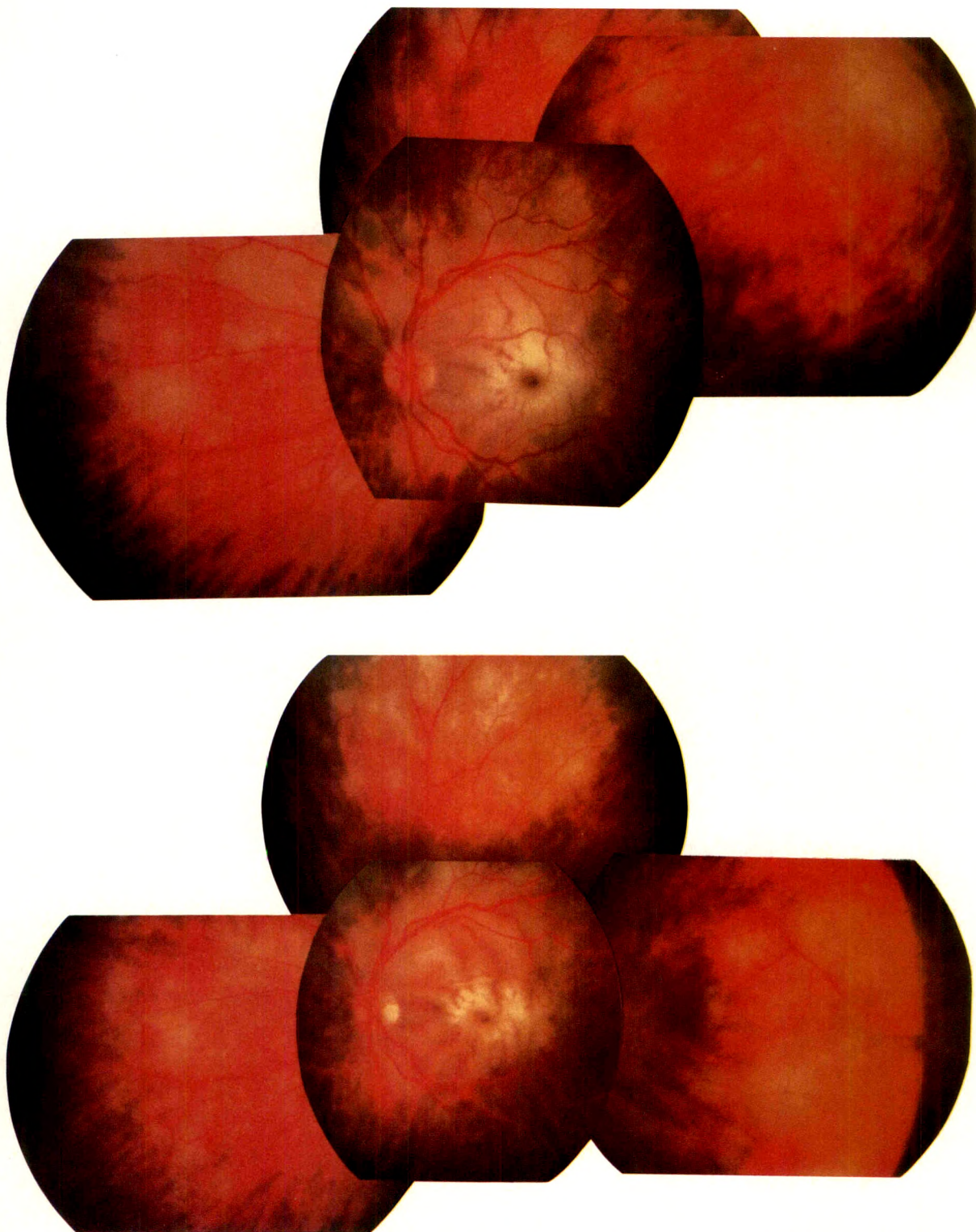
Five days later, the patient's visual acuity had decreased to finger counting at one foot in the right eye and no light perception in the left eye. The anterior segments remained free of inflammatory cells, but the macular regions appeared

more edematous. The posterior segments had almost confluent areas of deep retinal/choroidal whitening except around stretches of the vasculature where retinal edema appeared to be clearing (Fig. 2, bottom). Diagnostic enucleation of the left eye was performed and treatment with intravenous ganciclovir was initiated.

Bacterial cultures of the retina and choroid were positive for *M. avium* complex. Fungal cultures demonstrated no growth, and viral cultures for cytomegalovirus and herpes simplex virus were negative. Human foreskin fibroblast cultures showed typical cytopathic effect for varicella-zoster virus, and growth of varicella-zoster virus in these cells was confirmed by use of direct immunofluorescent staining with a monoclonal antibody to varicella-zoster virus. Indirect immunofluorescence with the same antibody demonstrated varicella-zoster virus antigen within cells of the outer nuclear layer. Examination of the tissue by transmission electron microscopy disclosed nonenveloped viral particles approximately 80 to 100 nm in diameter within the nuclei of photoreceptor cells (Fig. 3). Larger enveloped viral particles were observed as well. The size and shape of the viral particles were consistent with a virus of the herpesvirus family.

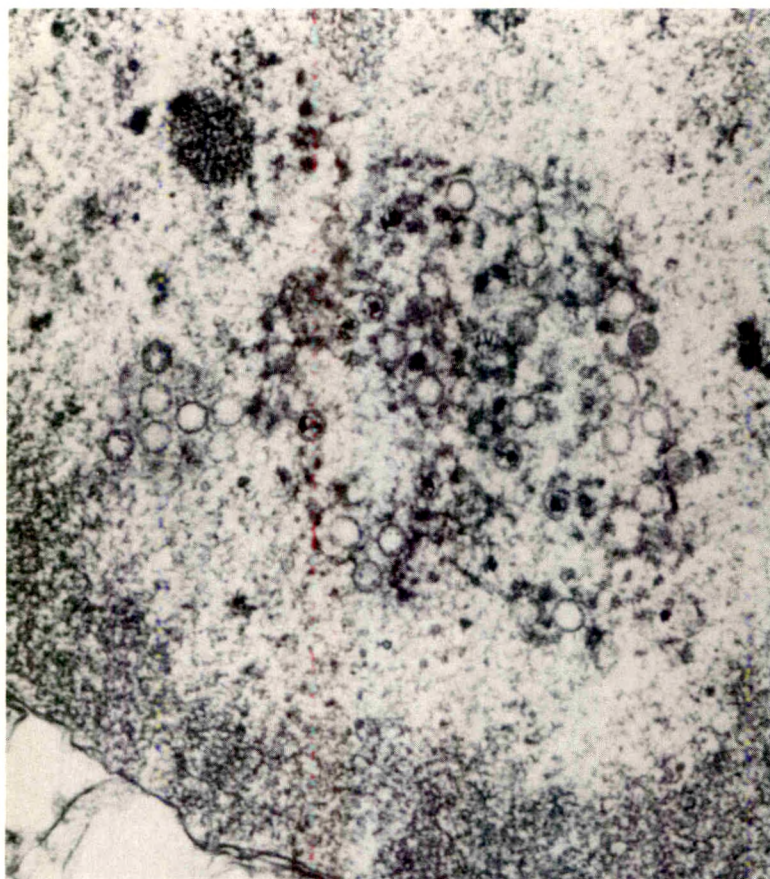
Light microscopic examination of the enucleated eye disclosed a clinically normal anterior





**Fig. 2** (Margolis and associates). Case 1. Top, left eye. Fundus photographs showing diffuse patchy choroidal/deep retinal inflammation and severe macular edema eight days after initial examination. Bottom, right eye. Fundus photographs showing progression of retinitis and clearing of perivascular retina five days later.





**Fig. 3** (Margolis and associates). Case 1, left eye. Transmission electron micrograph demonstrating enveloped and nonenveloped viral particles measuring 80 to 100 nm in diameter consistent with herpesvirus within the nuclei of photoreceptor cells ( $\times 40,000$ ).

segment except for a few lymphocytes in the ciliary muscle. The retina had a variable degree of inflammation and necrosis ranging from a clinically normal appearance to full-thickness necrosis (Fig. 4, left). A variable inflammatory response was observed in the choroid. In some areas, the choriocapillaries had an intense lymphocytic infiltrate, whereas in other areas, the lymphocytic infiltrate involved all layers of the choroid. In any given region of the fundus, the degree of choroidal inflammation was not related to the degree of retinal necrosis. In some regions of full-thickness retinal necrosis, the underlying choroid was free of inflammatory infiltrates. Necrosis and a marked lymphocytic infiltrate were also observed in the optic nerve (Fig. 4, right). No inclusion bodies were observed in the choroid, retina, or optic nerve. Similarly, no bacteria, fungi, or acid-fast organisms were observed in specially stained sections.

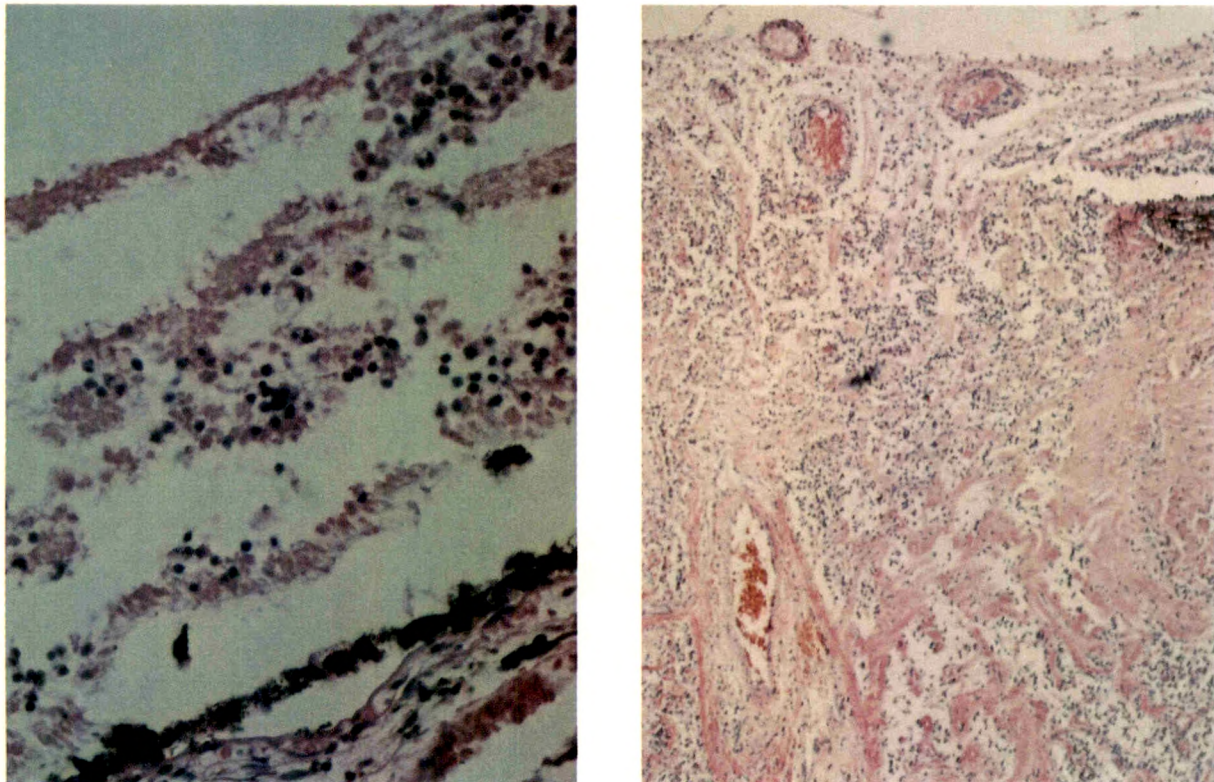
The patient's vision in the right eye contin-

ued to decrease despite antiviral treatment. Three weeks after enucleation of the left eye, the vision in the right eye had decreased to no light perception. Examination at this time disclosed no inflammatory cells in the anterior segment or vitreous, markedly attenuated retinal arteries, atrophy of the optic-nerve head, and a thin and atrophic retina with a few areas of pigmentary clumping.

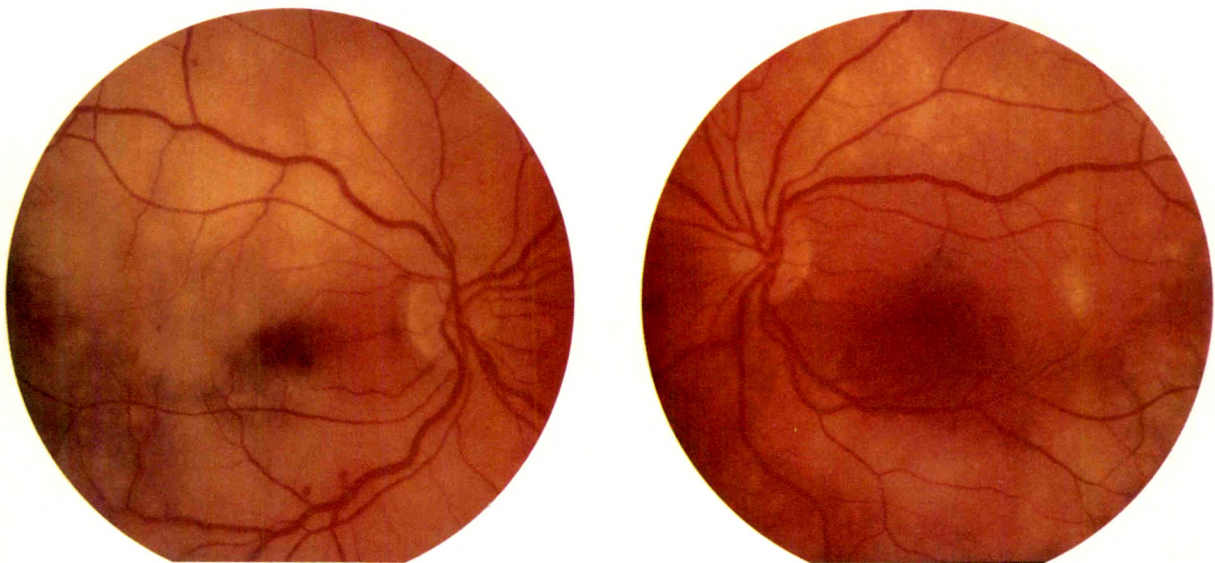
#### Case 2

A 35-year-old man with AIDS had progressive visual loss in his right eye. One year previously, he developed *P. carinii* pneumonia and was found to be seropositive for HIV. He also had multiple episodes of herpes simplex virus proctitis and molluscum contagiosum. Eight months before his ocular symptoms manifested, he was treated with oral acyclovir for herpes zoster ophthalmicus of the right eye. A maintenance dose of oral acyclovir (200 mg three times a day) was continued after resolu-





**Fig. 4** (Margolis and associates). Case 1, left eye. Left, Histologic section of the retina shows full-thickness necrosis (hematoxylin and eosin,  $\times 280$ ). Right, Necrosis is most prominent anterior to the lamina cribrosa and the nerve is heavily infiltrated with inflammatory cells (hematoxylin and eosin,  $\times 70$ ).



**Fig. 5** (Margolis and associates). Case 2. Left, right eye. Fundus photograph showing multifocal deep retina/choroidal inflammation and diffuse retinal edema involving the macula at initial examination. Right, left eye. Fundus photograph showing similar changes in the left eye but without macular involvement.



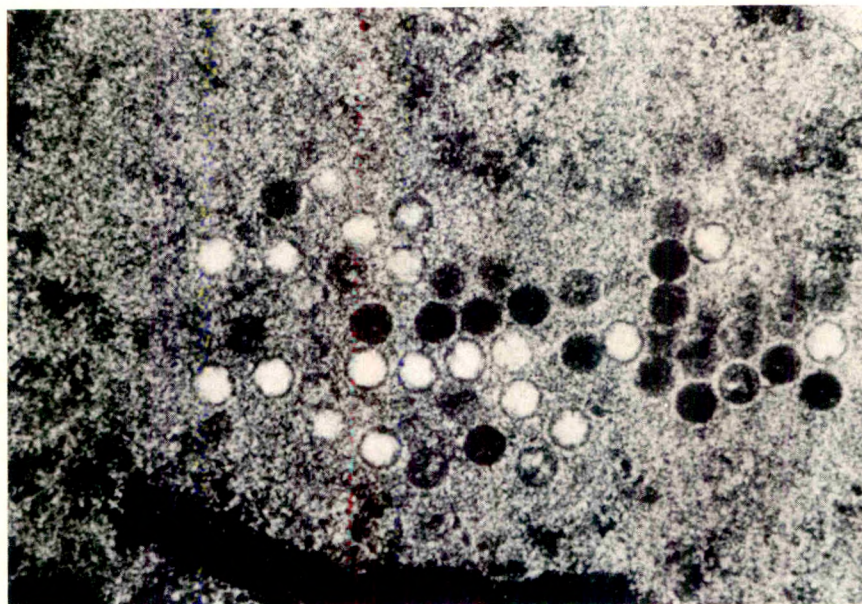


Fig. 6 (Margolis and associates). Case 2, right eye. Transmission electron micrograph demonstrates herpesvirus family particles within the outer nuclear layer ( $\times 80,000$ ).

tion of the acute eruption. Five weeks before the onset of his ocular symptoms, the dose of acyclovir was decreased to 200 mg twice daily because of mild gastrointestinal distress. Treatment with acyclovir was discontinued three weeks later when the patient developed numbness on the left side and profound hypokalemia.

Examination disclosed visual acuity of R.E.: 20/200 and L.E.: 20/20. A relative afferent pupillary defect was observed in the right eye. The anterior segments were clinically normal and there was no vitreitis. Multifocal deep retinal and choroidal lesions were observed bilaterally, and were worse in the right eye, where the central macula resembled a cherry-red spot (Fig. 5, left). In the left eye, there was sparing of the posterior pole within the temporal vascular arcades (Fig. 5, right). Treatment with intravenous acyclovir (8 mg/kg of body weight every eight hours) was initiated for a presumed diagnosis of varicella-zoster virus retinitis. Two days later, the acyclovir dosage was increased to 10 mg/kg of body weight every eight hours. Despite treatment, the disease continued to progress bilaterally, and vision in the right eye decreased to no light perception. Eight days after instituting treatment, a diagnostic enucleation of the right eye was performed. Viral cultures were positive for varicella-zoster virus and negative for herpes simplex virus and cytomegalovirus. Direct immunofluorescence staining disclosed varicella-zoster virus antigen within the retina but not

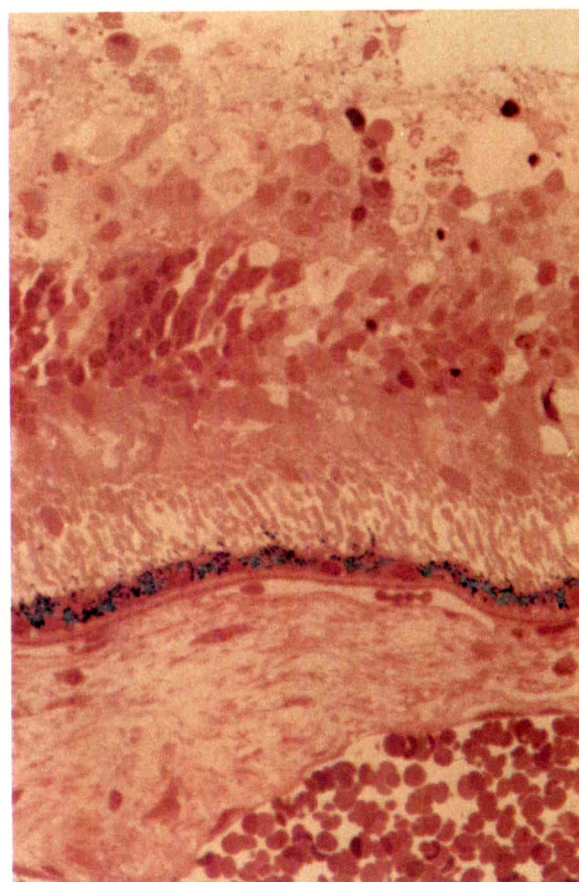
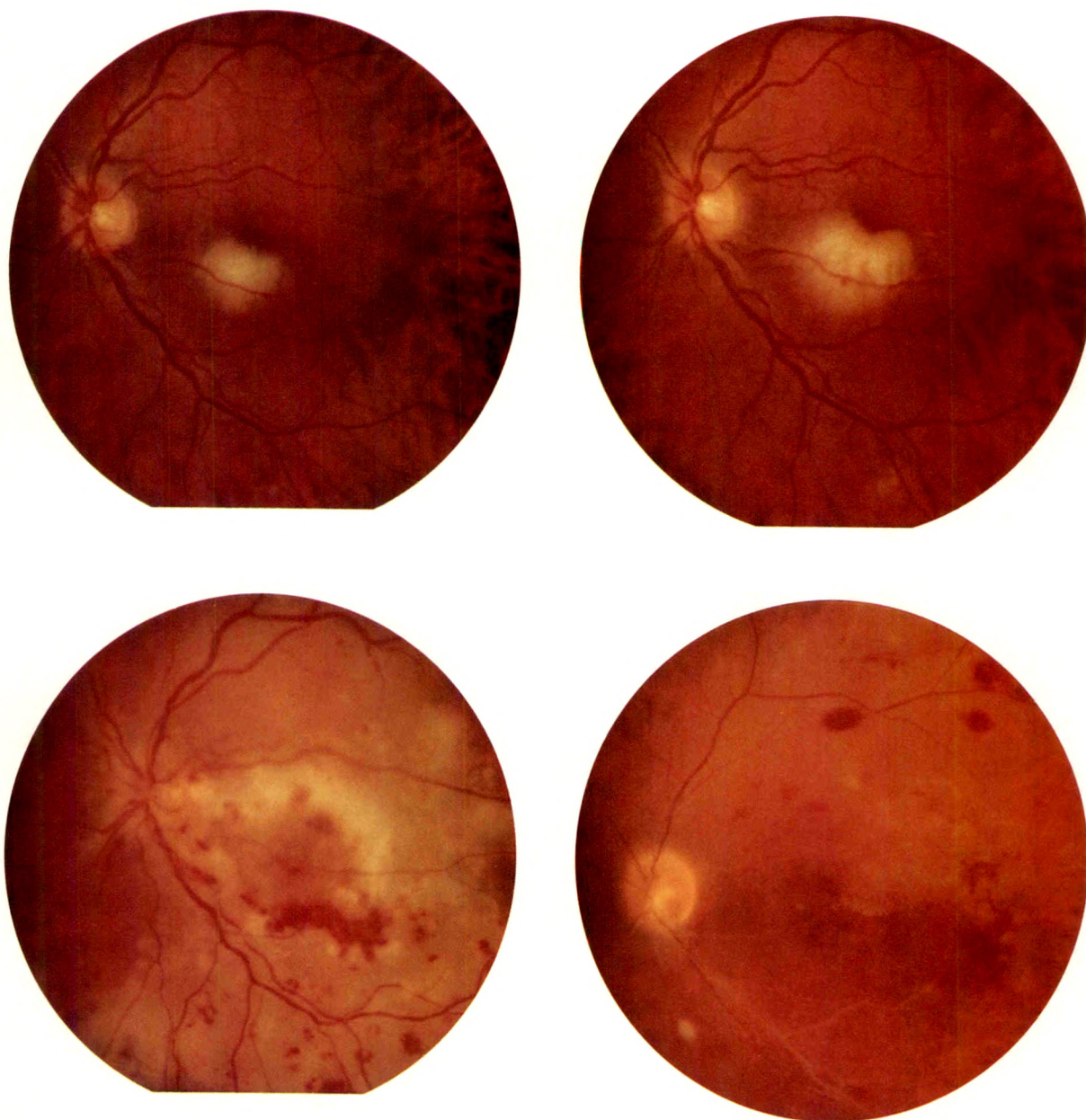


Fig. 7 (Margolis and associates). Case 2, right eye. Extensive retinal necrosis involving, in particular, the outer nuclear layer (toluidine blue,  $\times 700$ ). The underlying retinal pigment epithelium and choroid are clinically normal.





**Fig. 8** (Margolis and associates). Case 4, left eye. Top left, Fundus photograph showing focal retinitis inferior to fovea at initial examination. Top right, Fundus photograph showing progression of retinitis nine days later. Bottom left, Fundus photograph showing diffuse multifocal deep retinal inflammation and intraretinal hemorrhages three weeks after initial examination. Bottom right, Fundus photograph showing attenuated vessels and atrophic retina and nerve seven weeks after initial examination.

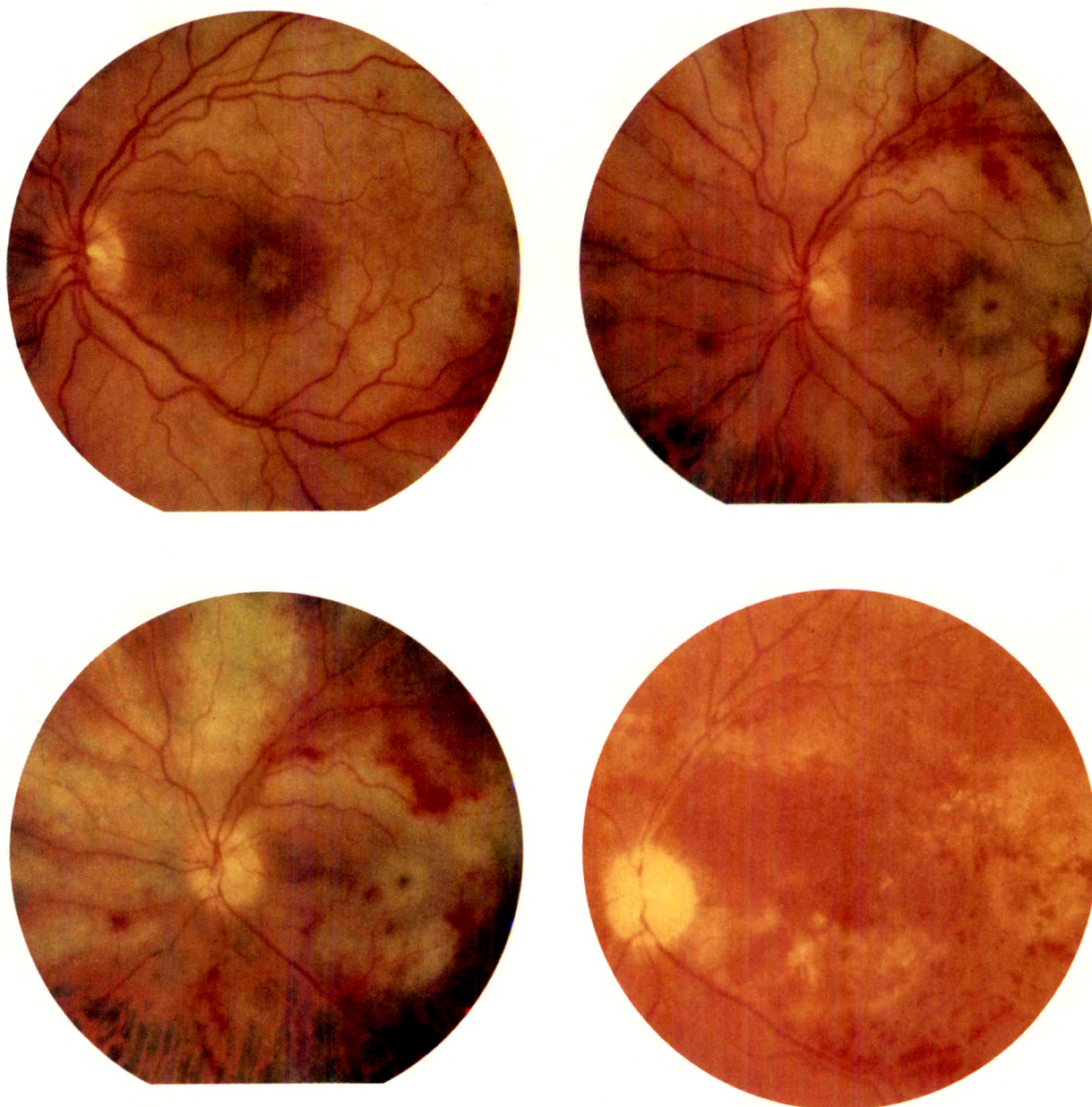
the choroid of the enucleated specimen. Examination of the tissue by use of transmission electron microscopy disclosed viral particles within the outer nuclear layer of the retina (Fig. 6). No viral particles were found in the choroid. The size and shape of the viral particles were consistent with those of the herpesvirus family.

Light microscopic examination of the enucleated eye disclosed a normal anterior segment and extensive necrosis of the retina (Fig. 7).

Necrosis was most marked in the outer nuclear layer. As in Case 1, a variable inflammatory response was observed in the choroid, but the degree of choroidal inflammation was not related to the degree of retinal inflammation. The optic nerve also demonstrated necrosis and a lymphocytic infiltrate. No inclusion bodies were observed in the choroid, retina, or optic nerve.

The dosage of intravenously administered





**Fig. 9** (Margolis and associates). Case 5, left eye. Top left, Fundus photograph showing opacification of the entire retina sparing the macula at initial examination. Top right, Fundus photograph taken six days later; the macula is involved and the perivascular retina has cleared. Bottom left, Fundus photograph showing further progression of retinal necrosis ten days after initial examination. Bottom right, Fundus photograph showing optic nerve pallor, attenuated vessels, and retinal atrophy one month later.

acyclovir was increased to 13 mg/kg of body weight every eight hours, with subsequent regression of the deep retinal/choroidal lesions temporal to the left macula. The administration of intravenous acyclovir was discontinued and the patient was being treated with oral acyclovir, 800 mg three times daily, at discharge. At this time, his visual acuity was 20/50 in the left eye. The anterior chamber and vitreous were

both free of inflammatory cells. Marked pallor of the optic nerve was observed. Two weeks later the patient's visual acuity decreased to 6/200 in the left eye and active retinochoroiditis was observed in the left macula. Despite continued treatment with oral acyclovir, visual acuity quickly decreased to no light perception. Four months later the patient died of aspiration pneumonia.

### Case 3

A 21-year-old HIV-infected man was seen because of distorted vision for three days. One week before the onset of his visual symptoms, he had an eruption of zoster dermatitis in a thoracolumbar distribution.

His visual acuity was R.E.: 20/25 and L.E.: 20/20. The anterior segment was clinically normal in both eyes. Examination of the fundus disclosed bilateral multifocal deep retinal/choroidal lesions of the posterior pole, with prominent perifoveal retinal edema and hyperemia of the optic-nerve heads. No vitreal cells were observed. Fluorescein angiography demonstrated early hyperfluorescence of the inflammatory lesions and late staining of the optic disks. No abnormalities of vascular filling were observed. Results of thoracic radiography, fluorescent treponemal antibody-absorbance test, antinuclear antibody, and a metabolic panel were all clinically normal. The erythrocyte sedimentation rate was 38, and the white blood cell count was 2,800 with a normal differential.

One week later, his visual acuity was 20/30 in both eyes. The anterior segment and vitreous humor of both eyes remained free of inflammatory cells, but the deep retinal/choroidal lesions and retinal edema had increased. The patient refused further diagnostic procedures and no treatment was instituted.

Over the next month, the disease progressed. Massive edema of the posterior pole caused the appearance of a cherry-red spot in both foveae, and the leading edge of the inflammation advanced steadily toward the periphery, leaving behind atrophic retina, attenuated vessels, and mottled pigmentation of the retinal pigment epithelium in both eyes. The vitreous humor remained clear in both eyes. Six weeks after the onset of symptoms, the patient had lost all light perception in both eyes and consented to further diagnostic tests. Blood cultures were positive for varicella-zoster virus, and varicella-zoster antigen was detected in a vitreal aspirate. No virus could be cultured from the vitreous humor. The patient died five months later.

### Case 4

A 36-year-old man with AIDS had sudden blurred vision in the left eye. The patient had had previous episodes of *P. carinii* pneumonia, histoplasmosis septicemia, candidiasis, central nervous system toxoplasmosis, recurrent perianal herpes simplex virus dermatitis, and thoracic zoster. Treatment in the past had included administration of zidovudine, amphotericin B, pentamidine, acyclovir, and a combination of

pyrimethamine and triple sulfonamides. Two months previously, he had cytomegalovirus retinitis, and worsening perianal herpes simplex virus dermatitis. The perianal lesions resolved with a ten-day course of oral administration of acyclovir, but the patient declined treatment for his cytomegalovirus retinitis. On the day the patient was first aware of ocular symptoms in his left eye, he also had sacral zoster dermatitis. Ocular examination disclosed a visual acuity of R.E.: 20/100 and L.E.: 20/70. The anterior segments and vitreous were free of inflammatory cells in both eyes. A single intensely white patch of retina was observed in the left perifoveal region. The surrounding retinal tissue was thickened, which caused the appearance of a cherry-red spot (Fig. 8, top left). Treatment with intravenous administration of acyclovir (300 mg every eight hours) and intravenous administration of clindamycin and trimethoprim-sulfamethoxazole for possible ocular toxoplasmosis was initiated. After six days of treatment, the patient had increased blood urea nitrogen and creatinine concentrations, and the acyclovir treatment was discontinued. Eight days later, his visual acuity had decreased to 20/80 in the right eye and 6/200 in the left eye. A relative afferent pupillary defect was observed in the left eye. The optic nerve of the left eye was hyperemic and retinal hemorrhages were observed. The anterior segment and vitreous humor of the left eye remained free of inflammatory cells. In the right eye, the cytomegalovirus retinitis had progressed to within 1 disk diameter of the macula. Treatment with intravenous administration of gancyclovir was instituted, and the visual acuity of the right eye stabilized at 20/60 for the next four months. In contrast, the visual acuity of the left eye rapidly decreased to light perception without projection. Repeated ophthalmoscopic examination of the left eye disclosed rapid progression of the posterior pole disease, leading to panretinal necrosis and atrophy (Fig. 8, top right, bottom left, and bottom right). The anterior segment and vitreous humor of the left eye remained free of inflammatory cells. Eight months after the onset of visual symptoms in the left eye, the patient died of malignant lymphoma and disseminated cytomegalovirus infection. Autopsy permission was obtained for all organs except the eyes.

### Case 5

A 45-year-old man without known medical problems developed vesicular skin lesions in the distribution of the first division of the right



trigeminal nerve and a severe keratouveitis in the right eye. The retinae of both eyes appeared clinically normal. Zoster ophthalmicus was diagnosed and serum analysis disclosed evidence of HIV infection. The skin lesions resolved without treatment, but a severe anterior uveitis persisted. Treatment with orally administered systemic prednisone (60 mg daily) had little effect on the ocular inflammation. Long-term treatment with orally administered acyclovir (200 mg five times a day) was initiated. Peripheral anterior synechiae formed, the anterior chamber angle closed 360 degrees, and the intraocular pressure could not be controlled. Within 18 months, the right eye had become hypotonus with complete loss of light perception. The left eye remained healthy.

Six months later, the patient had sudden onset of a painless, rapidly progressive loss in visual acuity of the left eye. Additionally, he observed loss of peripheral vision as though he were looking through a tunnel. He was still taking acyclovir orally, 200 mg five times a day. On examination, his visual acuity was 20/50 in the left eye with a markedly constricted visual field. A few cells were present in the anterior chamber and the vitreous humor was clear. There was deep homogenous opacification and thickening of the entire peripheral retina from the ora serrata to the posterior pole except for a region of the central macula (Fig. 9, top left). The optic disk was mildly hyperemic. Varicella-zoster virus retinitis as well as acyclovir-resistant herpes simplex virus retinitis were considered in the differential diagnosis. Treatment was begun with intravenous administration of vidarabine, 20 mg/kg of body weight/day, but there was no apparent effect on the retinitis. The entire retina, including the macula, became necrotic within the first week of treatment and all light perception was lost (Fig. 9, top right and bottom left). Three weeks later, the retinitis had largely resolved. The optic nerve was pale, the vessels were narrowed, and the retina was atrophic with areas of pigmentary clumping (Fig. 9, bottom right). There was no evidence of anterior chamber or vitreal inflammation.

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### Discussion

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These five patients with AIDS developed an unusual rapidly progressive retinitis (Table). All five cases were characterized by the development of early patchy choroidal and deep

retinal lesions succeeded by diffuse thickening of the retina. In all but one case, the retinitis began in the posterior pole with little or no clinical evidence of vasculitis. Optic nerve involvement, a cherry-red spot appearance of the macula, and early clearing of retinal whitening in a perivascular distribution were common features of these cases. All five patients had relentless progression of disease and were left with atrophic and necrotic retinae, pale optic-nerve heads, and narrowed vasculature. None of the patients developed aqueous or vitreal inflammation or retinal detachment. Three of the five patients had bilateral disease.

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See also p. 206

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Clinical and laboratory evidence suggest that varicella-zoster virus was the causal agent in all five cases. First, the onset of retinitis in four cases (Cases 2 through 5) either succeeded or was coincident with an eruption of dermatomal zoster. Second, varicella-zoster virus was cultured from the two chorioretinal specimens (Cases 1 and 2) and varicella-zoster virus antigen was detected in the vitreal aspirate from one case (Case 3). Third, by means of immunocytochemistry, varicella-zoster virus antigen was found in the outer retinae of both enucleation specimens. Fourth, viral capsids with the size and shape of herpesviridae were found in the outer retinae of both enucleation specimens.

Although these findings suggest that varicella-zoster virus has a role in retinitis, they do not prove causation. As many as 21% of all AIDS patients report a recent history of cutaneous zoster.<sup>2</sup> It is therefore possible that the relationship between dermatomal zoster and retinal disease in our patients was serendipitous. Additionally, because the biopsy specimens from our patients were obtained late in the course of the disease (with plenty of time for a primary process to trigger reactivation of varicella-zoster virus and subsequent transport of virus to the retina), the existence of varicella-zoster virus in these tissues might simply represent a late superinfection of the retina. However, the restricted distribution of capsids and antigen in the outer retina is consistent with the initial clinical observations of deep retinal disease and strongly suggests that varicella-zoster virus is the principal pathogen in this syndrome.

Of the previously described manifestations of zoster ophthalmicus, the syndrome described in this study most closely resembles acute retinal necrosis syndrome.<sup>3,4</sup> However, there are

**TABLE**  
**DISEASE CHARACTERISTICS OF VARICELLA-ZOSTER VIRUS RETINITIS ASSOCIATED WITH AIDS**

CASE NO.	EYES INVOLVED	CHARACTERISTICS OF EARLY LESIONS			EVIDENCE OF OPTIC NERVE INVOLVEMENT	VITREAL REACTION	ANTERIOR CHAMBER REACTION	DERMATOLOGIC INVOLVEMENT AND SITE	LABORATORY EVIDENCE OF VARICELLA-ZOSTER VIRUS*
		LOCATION	LAYER OF RETINA	CHERRY-RED SPOT					
1	Both	Macula	Outer	Yes	Autopsy	Trace	None	None	Positive retinal culture, immunocytochemistry (retina), electron microscopy
2	Both	Post-equatorial	Outer	Yes	Afferent pupillary defect, autopsy	None	None	Trigeminal (zoster ophthalmicus)	Positive retinal culture, immunocytochemistry (retina), electron microscopy
3	Both	Macula	Outer	Yes	Hyperemia	None	None	Thoracic, lumbar	Positive blood culture, immunocytochemistry (vitreous humor)
4	L.E.	Macula	Outer	Yes	Afferent pupillary defect, hyperemia	None	None	Sacral	NP
5	L.E.	Unknown	Outer	No	Hyperemia	None	None	Trigeminal (zoster ophthalmicus)	NP

\*NP indicates not performed.

some distinct differences between acute retinal necrosis syndrome and the disease observed in our patients. First, unlike acute retinal necrosis syndrome, there was little clinical evidence of iridocyclitis, vitreitis, or vascular sheathing in our patients. A second difference was the lack of early peripheral retinal disease in our patients. A third distinction was the cherry-red spot appearance of the maculae in our patients. Finally, our patients failed to develop tractional vitreal bands or retinal detachments as late complications of their disease, probably as a consequence of the scarcity of vitreal inflammation.

The patterns of disease observed in our patients also differed markedly from those described in three previously published case reports of zoster-related retinal disease in patients with AIDS.<sup>5-7</sup> In all three of these cases there was a close resemblance to acute retinal necrosis syndrome, and they were characterized by confluent peripheral whitening and a prominent vitreal reaction. Additionally, prominent vasculitis and late tractional detachments of the retina were features of two of these cases. Furthermore, the clinical pattern in our patients differed from that observed in two reported cases of zoster-related retinitis in immunocompromised patients not infected with HIV. One of these individuals, a patient with a

renal transplant, developed typical acute retinal necrosis syndrome.<sup>8</sup> The other individual, a patient undergoing chemotherapy for combined B-cell lymphoma and adult T-cell leukemia,<sup>9</sup> had pronounced vitreitis and retinal hemorrhages.

Varicella-zoster virus is capable of inducing a wide spectrum of clinical ocular disease not only in immunocompetent individuals, but in immunodeficient individuals as well. The degree of immunosuppression varies widely in patients with AIDS, and might account for the variability in clinical signs of zoster-related retinitis at initial examination in this population. Just as varicella-zoster virus may induce atypical skin lesions in patients with AIDS,<sup>10</sup> it may also produce novel patterns of clinical ocular disease. The scarcity of vitreal reaction and retinal infiltrates in our patients might be explained if our patients were all severely immunocompromised and unable to mount an efficient immune response to this pathogen. In contrast, HIV-infected patients who still have normal serum levels of circulating CD4 lymphocytes might have a typical acute retinal necrosis syndrome-like disease when infected with varicella-zoster virus.

One interesting feature of the patients described in this study was the associated optic nerve disease. Relative afferent pupillary de-



fects were observed in two patients, the optic nerve head was hyperemic in two other patients, and extensive inflammation of the posterior optic nerve was observed in both disease specimens. Involvement of the optic nerve is a common feature of acute retinal necrosis syndrome,<sup>11-13</sup> as well as of varicella-zoster virus-related ocular disease in patients with AIDS.<sup>14,15</sup> Because recent reports by Winward, Hamed, and Glaser<sup>7</sup> and Sergott and associates<sup>11</sup> suggest that immediate recognition and treatment of varicella-zoster virus optic neuritis in both immunocompetent and AIDS patients may help to preserve vision in these individuals, varicella-zoster virus-related retinal disease should be considered in the differential diagnosis of any unusual retinitis accompanied by optic nerve involvement.

Another interesting feature of these cases was the unusual perivascular pattern, resembling cracked mud, that appeared relatively early in the course of the disease. Forster and associates<sup>1</sup> interpreted these findings as regions of perivascular retinal sparing. Study of our patients, however, suggested that this pattern represents early removal of necrotic debris or edema from retinal tissue adjacent to the vasculature (Figs. 2 and 9).

The cases of varicella-zoster virus retinitis in this study were readily distinguished from cytomegalovirus retinopathy on the basis of several clinical features. Unlike cytomegalovirus retinopathy, these cases were all multifocal, rapidly progressive, and associated with diffuse deep retinal opacification without granular borders. Furthermore, in contrast to cytomegalovirus retinopathy, early foveal involvement was characteristic in our cases. It is important to distinguish between these two viral retinopathies in order to establish optimal treatment strategies.

Standards for the appropriate treatment of AIDS patients with suspected varicella-zoster virus retinitis have yet to be firmly established. Nonetheless, we recommend the use of intravenously administered antivirals in these patients because both acyclovir and vidarabine have been shown to be effective in the management of varicella-zoster virus in immunocompromised patients.<sup>16-18</sup> The use of antivirals in these individuals serves not only to treat the ocular disease, but to prevent the central nervous system complications that may develop as a result of viral spreading along the optic or trigeminal nerves.<sup>19,20</sup> Furthermore, in view of the additive effects of acyclovir and vidarabine

against varicella-zoster virus,<sup>21</sup> and the increasing incidence of acyclovir resistance in varicella-zoster virus isolates from patients with AIDS,<sup>22</sup> there may even be a rational basis for the combined use of these two drugs in the treatment of rapidly progressive varicella-zoster virus retinitis. The possible need for combined antiviral treatment is highlighted by a recent report by Moriyama and associates<sup>9</sup> of a case of disseminated zoster with retinitis that required combined vidarabine and acyclovir treatment.

In the immunosuppressed individual, the generally accepted dosage of intravenously administered acyclovir for the treatment of varicella-zoster virus infection is 10 mg/kg of body weight every eight hours and 10 mg/kg of body weight/day of vidarabine. The course of treatment may be long. Blumenkranz and associates<sup>23</sup> found that regression of acute retinal necrosis syndrome in immunocompetent individuals treated with intravenously administered acyclovir was a slow process. An average of 3.9 days of treatment was required until the earliest clinical signs of regression were observed, and completion of treatment required an average of 32.5 days. An even longer time interval might be expected in immunocompromised patients. Several of our patients received treatment with antivirals, but with little benefit. We believe that these patients would have benefited from appropriate antiviral treatment, but were treated with either inadequate doses or were treated too late in the course of infection.

As the life expectancy of HIV-infected individuals increases through aggressive management of opportunistic infections, we are likely to see an increased incidence of this clinical manifestation of varicella-zoster virus.

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## Antibody Indications of Secondary and Superimposed Retinal Hypersensitivity in Retinitis Pigmentosa

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**Antibody reactions with recognized retinopathy-inducing retinal antigens may be interpreted to reflect ongoing autoimmune events responsible for some forms of vision loss. We sought evidence of secondary and superimposed retinal hypersensitivity indicated by such antibody reactivity in a random group of patients with retinitis pigmentosa. We identified patterns of immunologic reactivity within members of a group of 52 patients with retinitis pigmentosa, which suggests some patients with retinitis pigmentosa may experience consequential superimposed retinal hypersensitivity. Identifying subgroups of patients with retinitis pigmentosa who exhibit indications of retinal hypersensitivity to known uveitopathogenic retinal proteins may permit the reduction of their rate of retinal degradation by immunomodulation.**

**I**NHERITED HUMAN pigmentary retinopathies, consisting of at least 14 subgroups, are gathered under the common term of retinitis pigmentosa.<sup>1</sup> Noninherited pigmentary retinopathies, resulting from latent infections or trauma, may be misdiagnosed as retinitis pigmentosa when they have similar signs and

symptoms at initial examination. Efforts to group patients on the basis of inheritance have, in the past, been hindered by difficulties in obtaining family histories. Retinitis pigmentosa is more commonly identified and classified by means of morphologic and electrophysiologic criteria.<sup>1-6</sup> Recently, advances in identifying the chromosomal location of mutations associated with autosomal and x-linked retinitis pigmentosa have introduced the means to study inheritance patterns with great precision.<sup>7</sup> However, the methods of chromosomal analyses are complex and not widely available. Additionally, the chromosomal aberrations associated with the different forms of retinitis pigmentosa have yet to be fully defined.<sup>8</sup> Mutations in the rhodopsin gene and other retinal enzyme deficiencies are suspected because vision loss in retinitis pigmentosa is related to alterations in photoreceptor cells and pigment epithelium that use unique metabolic pathways.<sup>9-11</sup>

The degenerating retina may leak organ-specific antigens into the bloodstream, a process by which the host may possibly become sensitized to antigens formally confined within the globe.<sup>12</sup> Retinitis pigmentosa-related retinal degradations may therefore initiate superimposed and secondary immune-mediated events, a form of contributory epiphenomena, which could hasten the destruction of the retina.<sup>13-24</sup> Both humoral and cellular components of the immune system are suspected of augmenting retinal degradation as secondary contributory events.<sup>24-29</sup> Immunologic reactions with the three known uveitopathogenic retinal proteins (rhodopsin, interphotoreceptor retinoid-binding protein, and the retinal S-antigen) may indicate the patient is undergoing autoimmune reactions similar to those described in sensitized animals.<sup>30</sup> We have sought evidence of immunologic hypersensitivity to these antigens in 52 patients with primary retinitis pigmentosa at initial examination. These patients had no family history of retinopathy and no known

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secondary infections or disease. Antibody assays were performed at the time of examination and serum samples were stored for comparative analyses. Retinal antibody reactions within the group of patients with retinitis pigmentosa were examined to determine the degree of diversity each member exhibited and the results were compared with those obtained from clinically normal individuals. We recorded patterns of common immunologic reactivity in order to identify the most frequently involved retinal antigens in retinitis pigmentosa and to evaluate any incidence of autoantibody involvement with the three known uveitopathogenic retinal antigens. Findings indicated that patients with retinitis pigmentosa may be segregated into groups according to their immunoreactivity with known retinopathy-inducing retinal antigens.

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### Material and Methods

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**Retina extract**—A preparation of pooled retinal proteins for antigen analysis was made from a saline-soluble extract of bovine retina as described by Wacker and associates.<sup>30</sup> After centrifugation, the retina extract was standardized to contain 10 mg/ml of protein and was stored for use at  $-20^{\circ}\text{C}$ .

**Serum samples**—Serum samples were obtained from 52 patients who had primary retinitis pigmentosa diagnosed. The majority of the patients were women, the average age was 45 years, and the average onset of retinitis pigmentosa was at 25 years of age. Serum samples from these patients were stored for study at  $-20^{\circ}\text{C}$  in an equal volume of phosphate-buffered saline solution, polysorbate-20, and bovine serum albumin (0.1M phosphate-buffered saline solution; 0.05% polysorbate-20; 1 mg/ml of bovine serum albumin; and 0.01% sodium azide; pH, 7.5). For comparison controls, antibody reactions within the group of patients with retinitis pigmentosa were compared with one another in order to provide internal controls within the same disease. The results were related with those observed in serum derived from six clinically normal individuals.

**Western immunoblot analyses**—Western immunoblot analysis procedures were performed, using conventional methods.<sup>31-34</sup> The retina extract (1.0 ml) was electrophoretically separated in 1.5-mm thick, 20-cm gels, and transferred to

nitrocellulose from which 4-mm-wide strips were cut. The strips were blocked in 0.5% nonfat milk in phosphate-buffered saline solution before reaction with the patient's serum. All sera were assayed at a dilution of 1:200. Serum antibody binding was detected autoradiographically through the application of  $^{125}\text{I}$ -labeled goat anti-human IgG. The relative molecular weight of retinal proteins that bound antibodies were analyzed in side-by-side comparisons to identify common immunologically reactive proteins. Molecular weight approximations were made by comparisons with pre-stained molecular weight markers (Sigma Chemical Company, St. Louis, MO, product No. SDS-7B).

**Peptide synthesis**—Peptides corresponding to the N-terminal and C-terminal 15 amino acids of bovine photoreceptor S-antigen were synthesized manually, using the solid-state method of Hodges and Merrifield<sup>35</sup> as modified by Gorman,<sup>36</sup> except that cleavage of peptides and protecting groups was performed by treatment with hydrogen bromide and anhydrous trifluoroacetic acid. Peptides were purified and quantified as previously described.<sup>37</sup>

**Radioimmunoassay with peptides**—Serum from the group of retina-reactive patients was assayed by using peptide fragments of the retinal S-antigen as the test antigen.<sup>35-39</sup> Patients with retinitis pigmentosa who showed no Western immunoblot analysis reactivity with retina were included with clinically normal subjects as comparison controls. Assay procedures were performed on the basis of the principles described by Suter.<sup>38</sup> Synthesized peptides were bound to glutaraldehyde-coated tubes, which were then blocked with 5% nonfat milk in phosphate-buffered saline solution to prevent nonspecific binding. Each patient's serum was assayed at a final dilution of 1:100 and incubated overnight at  $22^{\circ}\text{C}$ . The tubes were then washed three times with 10 mM of Tris-HCl (pH, 8.0) containing 0.05% polysorbate-20, and twice with water. Finally, samples were reacted for one hour at  $22^{\circ}\text{C}$  with  $^{125}\text{I}$ -protein A (approximately 200,000 cpm per tube), washed three times, and counted in a gamma counter.

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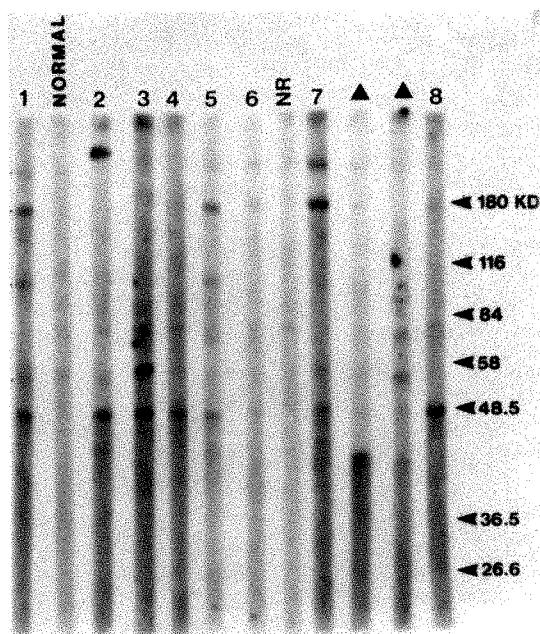
### Results

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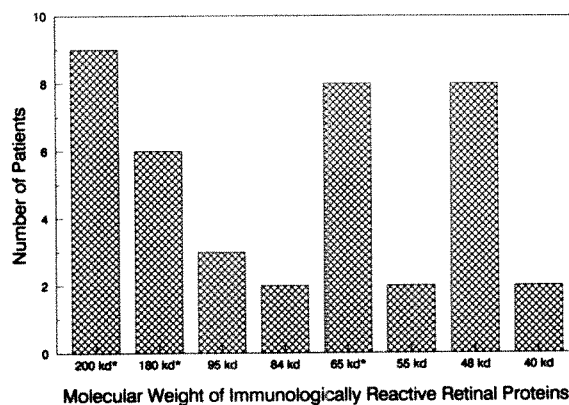
After initial antibody screening by enzyme-linked immunosorbent assay,<sup>40</sup> 41 samples were



excluded from further study because they gave serologically normal or weak reactions with retinal antigens. The remaining 11 sera exhibited a minimum of twice the clinically normal reactivity with retinal antigens when assayed by the ELISA. Western immunoblot analysis of the 11 immunologically reactive patients with retinitis pigmentosa on retinal antigens disclosed a variety of antibody responses, the most common approximating 48 kd where the retinal S-antigen is found<sup>41</sup> (Fig. 1). Additionally, two patients possessed antibodies reactive with a 40-kd antigen, which may be rhodopsin.<sup>22</sup> No immunologic reactions were found with antigens in the molecular weight range of 140 kd<sup>12</sup> in which the interphotoreceptor retinoid-binding protein is found. Other retinal proteins bound only by sera from the patients with retinitis pigmentosa were roughly 95, 84, and 55 kd. Clinically normal pooled serum used as a



**Fig. 1** (Thirkill and associates). Western immunoblot analysis assay reacting serum from the group of eight, S-antigen-reactive patients with retinitis pigmentosa, on electrophoretically separated protein components of solubilized extract of bovine retina, identified by numbers as 1 through 8. Clinically normal and nonreactive (NR) patients are included for comparison. All sera reacted at a dilution of 1:200. The retinal S-antigen is located at the 48.5-kd marker. Additionally, two patients (triangle) may be reacting with rhodopsin at approximately 40 kd. Note variations in intensity of antibody reactions with common antigens.



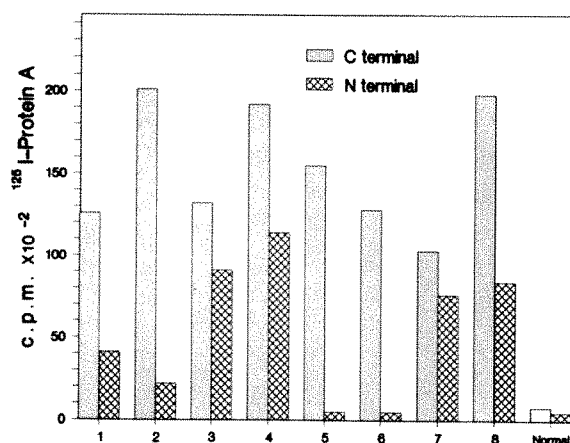
**Fig. 2** (Thirkill and associates). The incidence of immunologic involvement of eight predominating retinal proteins (each identified by their relative molecular weight) is indicated by the number of patients showing antibody reactivity with each. Serum antibodies were assayed at a final dilution of 1:200. Asterisk indicates retinal antigens weakly reactive with pooled clinically normal serum.

comparison control did not react with retinal proteins at the described dilution of 1:200. Common immunologic reactions are illustrated in Figure 2, which shows the number of patients with retinitis pigmentosa whose serum reacted with the predominating immunologically reactive retinal antigens resolved in the Western immunoblot antibody assays.

Radioimmunoassays using synthesized C- and N-terminal fragments of the photoreceptor S-antigen confirmed the observations made by Western immunoblot analysis by verifying that the eight patients who were reactive with a retinal protein of the appropriate molecular weight in the Western immunoblot assays were in fact reacting with the retinal S-antigen. Results showed that the eight selected patients with retinitis pigmentosa had stronger immunologic interactions with the synthesized C-terminal fragment compared with that observed with the N-terminal fragment (Fig. 3).

## Discussion

Eight of the 11 patients with immunologic-reactive retinitis pigmentosa possessed antibodies to the retinal S-antigen, which may indicate their loss of tolerance to this important retinal protein. This antibody reaction suggests the possibility of autoimmune reactions as contributing factors, superimposed on, and en-



**Fig. 3** (Thirkill and associates). Eight patients with retinitis pigmentosa were chosen because of their immunoblot reactivity with a retinal protein antigen exhibiting the migratory characteristics of the retinal S-antigen. The antibody activity of sera from these eight patients was compared by radioimmunoassay with nonreactive patients with retinitis pigmentosa and pooled clinically normal sera on the antigens of synthesized C and N-terminal fragments of the photoreceptor S-antigen. Variations in antibody titer to the antigenic fragments were evident in the selected group of eight. Other members of the retinitis pigmentosa study group and clinically normal pooled human sera were found to be nonreactive with the synthesized peptides. All were assayed at a dilution of 1:100.

hancing the progress of their retinopathies.<sup>20-23,25-27</sup> Experimental animal models of autoimmune ocular inflammations illustrate the severe pathologic effects that result from immunologic hypersensitivity to specific ocular antigens.<sup>42-44</sup> The ease with which tolerance to specific retinal proteins may be broken and experimental retinopathies induced in laboratory animals is an indication of the delicate balance that separates an effective defense system from a detrimental autoimmune response.

Rhodopsin (40 kd),<sup>42</sup> the interphotoreceptor retinoid-binding protein (140 kd),<sup>44</sup> and the photoreceptor S-antigen (48 kd)<sup>30</sup> are the only known experimentally uveitogenic retinal proteins, although others almost certainly exist. All three proteins can be isolated in pure form and induce related autoimmune ocular inflammations in experimental animals which can be transferred to other animals with activated lymphocytes.<sup>42,45-48</sup> These characteristics fulfill all the criteria for autoimmune involvement as described in Witebsky's postulates, which characterize a true autoimmune disease.<sup>49</sup>

Only two of our patients' sera bound a retinal protein in the size range approximating 40-kd molecular weight. This retinal protein may be rhodopsin, which migrates to this site in the reducing acrylamide gels we used. Recent evidence of rhodopsin loss in retinitis pigmentosa suggests that this photoreceptor component may be one of the first to be destroyed in the retinopathy process.<sup>7</sup> None of the patients in this study reacted with any retinal protein in the range of 140 kd at which the interphotoreceptor retinoid-binding protein would be found, leaving the retinal S-antigen as the most commonly involved in this study group. The other three as yet unidentified retinal proteins reactive with serum antibodies exclusively in the patients with retinitis pigmentosa were 95, 84, and 55 kd in size (Fig. 2). Internal controls, obtained by comparing the positive findings with those obtained from nonreactive members of the retinitis pigmentosa group and clinically normal sera, serve to demonstrate the relevance of the abnormal immunoreactivity in the retina reactive group.

The antigenic dissection and nucleic acid sequencing of the photoreceptor S-antigen has characterized the fragments of the molecule that are responsible for the induction of experimental uveitis.<sup>39</sup> The immunologic dissection of the S-antigen molecule, using highly specific monoclonal antibodies reactive with single epitopes, provides valuable information on the antigenic character of the whole tertiary structure.<sup>39,50</sup> Small peptide fragments of the S-antigen, consisting of a few amino acids, have been demonstrated to induce an immune response leading to ocular inflammations.<sup>51</sup> The radioimmunoassays performed in this study indicate an immunologic bias in the patients with retinitis pigmentosa we studied. Antibody interactions predominated in the C-terminal region of the molecule, where the majority of uveitopathogenic sites have been mapped.<sup>50</sup>

Although the pathologic relevance of retina autoantibodies in patients with retinitis pigmentosa is still the subject of much debate, a demonstrable degree of immunologic hypersensitivity to recognized uveitopathogenic antigens should not be discarded as irrelevant to the disease process. We suggest that patients with retinitis pigmentosa who have indications of immunologic hypersensitivity to known uveitopathogenic retinal antigens at initial examination are at higher risk to autoimmune retinopathies and should be treated accordingly. Subgroups of autosomal dominant retinitis pig-



mentosa have been shown to have mutations in rhodopsin and have been categorized as rhodopsin autosomal dominant retinitis pigmentosa.<sup>8</sup> The eight patients in this study who exhibited indications of hypersensitivity to the retinal S-antigen may accordingly be identified as S-antigen reactive retinitis pigmentosa. Appropriate treatment, including the manipulation of the immune response, might alter the course of their condition and possibly reduce the rate of retinal deterioration.

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# Randomized, Double-Masked Study of Cyclosporine Compared to Prednisolone in the Treatment of Endogenous Uveitis

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Fifty-six patients with bilateral sight-threatening noninfectious intermediate or posterior uveitis participated in a randomized double-masked study of the use of cyclosporine vs prednisolone in their treatment. Applying the end-point definitions, visual acuity or vitreal haze improved in only 13 of 28 (46%) patients in each group. The macular edema resolved in seven of 15 patients of the cyclosporine-treated group, and in ten of 16 patients of the prednisolone-treated group ( $P = .376$ ). Patients whose therapies failed both cyclosporine and prednisolone trials were treated with both drugs, which resulted in additional patient improvements. Secondary effects were observed in both therapeutic alternatives, the most notable being alterations in serum creatinine concentration and hypertension with the dosage of cyclosporine used.

**T**HE MECHANISMS of many intraocular inflammatory conditions continue to undergo scrutiny, resulting in an increased appreciation of their complexities. Improving therapeutic alternatives in the treatment of uveitis is an ever-evolving process. While inflammatory infectious conditions can be approached with specific antimicrobial therapy, a large group of ocular inflammatory disorders are usually considered

results of endogenously induced dysregulation. These are usually treated with nonspecific anti-inflammatory or cytotoxic agents, most notably prednisone and alkylating agents.<sup>1</sup>

With the advent of reliable animal models for the study of uveitis,<sup>2-4</sup> the factors leading to ocular inflammation can begin to be dissected. These models demonstrate the importance of the T-cell networking in the development of disease,<sup>5</sup> and lead to the logical prediction that a drug with predominantly anti-T-cell effects, such as cyclosporine, could be a potential addition to the therapeutic regimen. Our initial nonrandomized experience with this agent has already been reported,<sup>6,7</sup> and reports describing double-masked randomized studies demonstrating the efficacy of cyclosporine as opposed to the various immunosuppressive agents (colchicine, alkylating agents) in the treatment of ocular manifestations of Behçet's disease have appeared.<sup>8,9</sup> However, the use of corticosteroids remains the preferred treatment for the vast majority of noninfectious uveitides in the United States. Therefore, we performed a randomized double-masked study to compare the use of cyclosporine compared to the use of systemic corticosteroids in the treatment of noninfectious intermediate and posterior uveitis (excluding Behçet's disease) in an American clinic. Because both agents were used as the sole anti-immunosuppressive agents, their relative efficacies were more clearly observed.

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## Patients and Methods

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After obtaining approval from the Institute review board and the Clinical Center at the National Institutes of Health, 56 patients (36 females, 20 males) with intermediate or posterior noninfectious uveitis were entered into the

**TABLE 1**  
**DIAGNOSES OF PATIENTS IN RANDOMIZED**  
**CYCLOSPORINE/PREDNISOLONE STUDY**

DIAGNOSIS	CYCLOSPORINE	PREDNISOLONE	TOTAL
Pars planitis	8	13	21
Intermediate uveitis (Non pars planitis)	7	8	15
Sarcoid uveitis	5	2	7
Birdshot retinocho- roidopathy	2	3	5
Vogt-Koyanagi- Harada's disease	2	1	3
Posterior uveitis	2	1	3
Diffuse retinal vasculitis	2	0	2

study (Table 1). The mean age was 38 years (range, 10 to 61 years). Patients were eligible for the trial if they (1) were 10 years of age or older, and were capable of understanding the goals of the project; (2) had active bilateral disease with a visual acuity of 20/40 or worse in both eyes because of intraocular inflammation (active inflammation was defined as a recent [within four months] decrease of two or more lines of visual acuity or active retinal lesions or vitreal haze); and (3) had no underlying chronic infectious disorder, major organ dysfunction, or history of neoplasia.

Patients were not considered for the trial if: (1) they anticipated ocular surgery within the first six months of the study; (2) they had been treated for ocular disease with systemic corticosteroids or cytotoxic agents for at least one month before entering the study; (3) they had insulin-dependent diabetes or uncontrolled systemic hypertension with a diastolic pressure greater than 90 mm Hg on two occasions; or (4) a female patient was pregnant (females of childbearing age were required to use an accepted method of contraception).

Patients meeting these criteria were then randomized to one of two therapies. In brief, patients were randomized to using prednisolone or cyclosporine as their sole systemic therapeutic agent for treatment of their uveitis. Topical medication could be used any time during the study. The prednisolone was prepared (by the drug development group of the National Institutes of Health Clinical Center Pharmacy) into a liquid solution that had the taste and consistency of the cyclosporine liquid preparation. This made it impossible for the patients to know which drug they were taking on the basis

of physical characteristics of the two preparations. Patients were given a dose of prednisolone (64 mg) that was pharmacologically equivalent to 80 mg of prednisone if they weighed 70 kg or more, or the equivalent of 60 mg of prednisone (42 mg of prednisolone) if they weighed less than 70 kg. Patients randomized to the cyclosporine alternative of the study received 10 mg/kg of body weight/day as a starting dosage. Dosage of each therapeutic alternative depended on the clinical status of the patient. The dosage of cyclosporine could be as high as 15 mg/kg of body weight/day, but only for a short interval. The maximal dose of prednisolone was the prednisone equivalent of 80 mg/day for all patients in that therapeutic alternative.

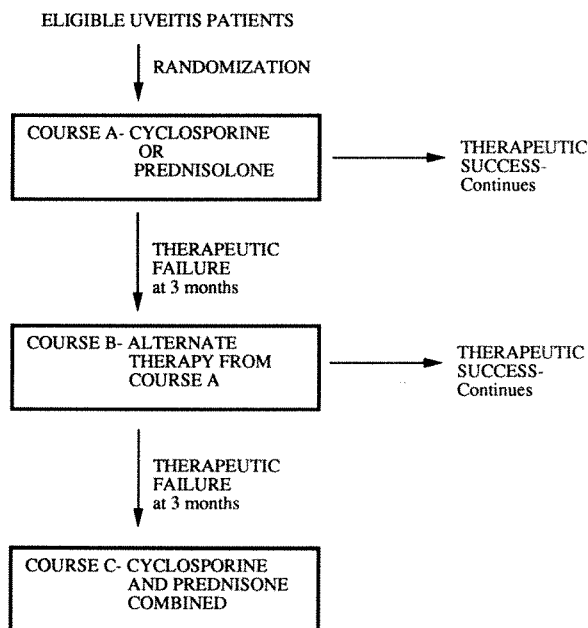
Patients returned at monthly intervals during the first three-month period (termed Course A), and were evaluated ocularly by two masked observers who had to agree on the ocular findings. Several ocular values were measured during each visit, including anterior chamber cell and flare, vitreal cells and haze (the latter measured by standardized photographs<sup>10</sup>), macular edema, and vascular sheathing. Further, the best visual acuity at baseline and at subsequent visits was measured by a masked individual by use of the Early Treatment of Diabetic Retinopathy Study chart.<sup>11</sup> The number of letters read at 4 meters was corrected by adding 30 so that it could be linearly compared with visual acuities taken at 1 meter. Therefore, a score of 5 is a visual acuity of 5/200, and a score of 85 is 20/20.

The first endpoint of this study was at three months. The definition of therapeutic success for this study at that time was an improvement in visual acuity of 15 letters (three lines) or more in at least one eye, or an improvement of at least two increments on the vitreal haze scoring scheme.<sup>12</sup> Additionally, patients taking prednisolone could take no more than 20 mg/day at the three-month evaluation. This amount or one lower was considered a dose that could be given for an extended period of time. Patients were considered therapeutic failures before the three-month endpoint evaluation if, after maximal therapy of one week, the visual acuity in one eye decreased ten letters (two lines) from baseline value; or if the disease appeared to be progressing into the macula, leading to permanent loss of vision; or if there was uncontrolled systemic hypertension, diabetes, ulcer, or impaired hepatic function. A serum creatinine concentration of 2.0 mg/dl



and a glomerular filtration rate of 50 ml/minute or less necessitated a decrease in the therapeutic dose.

At the three-month juncture, patients deemed therapeutic successes on the basis of the above criteria remained on the therapy to which they were initially randomized, and were evaluated every three months for one year (Fig. 1). However, if the patients did not meet these criteria, they were crossed over to the alternative therapy, that is, from cyclosporine to prednisolone treatment and vice versa. This was designated as Course B. Patients were then treated with the medication as in Course A, and were evaluated at three months after the initiation of Course B, applying the same success criteria. Those patients in whom therapy resulted in an improvement of 15 letters or two increments in vitreal haze were considered a success and were continued for one year, with examinations at three-month intervals. Those patients whose therapies did not meet the success criteria were then assigned to Course C, which was a combination of cyclosporine (average dose, 8.1 mg/kg of body weight/day) and prednisone treatment (average dose, 10 to 30 mg/day). The criteria for early termination of participation in the study as outlined in Course A were also applied to Courses B and C.

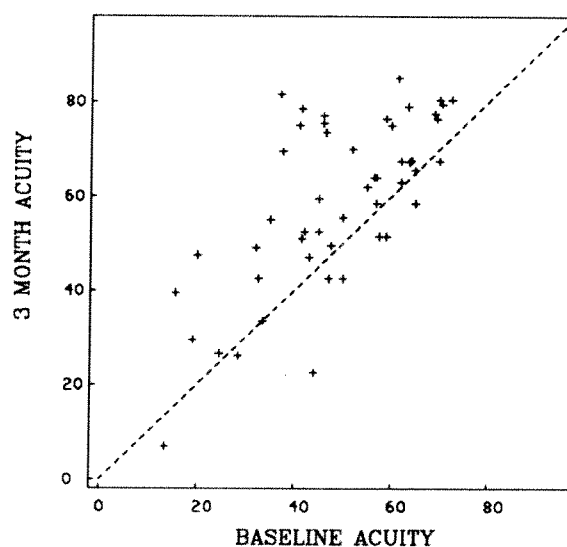


**Fig. 1** (Nussenblatt and associates). Treatment scheme with possible options in this randomized study of the use of prednisolone and cyclosporine in the treatment of endogenous uveitis.

## Results

A total of 56 patients were entered into the trial, with 28 patients entered into each therapeutic alternative (Table 1). Of the 56 patients, 36 (64%) had intermediate uveitis. A reasonably equal distribution of the various entities to the two therapeutic alternatives was accomplished, and the pretherapeutic visual acuities of the two randomized groups were similar. The average baseline visual acuity for the cyclosporine-treated group was 48.4 letters, and 51 letters for the prednisolone-treated group, both values corresponding to an approximate visual acuity of 20/100.

Three months after the initiation of therapy, the vast majority of patients in both therapeutic alternatives had an improvement in visual acuity as compared with the baseline value (Fig. 2). Six patients were therapeutic failures before three months and so provide no data for the three-month visit on Course A. However, applying the primary endpoint definitions for therapeutic success, a comparison between the two therapies may be made (Table 2). For Course A, all the therapies of the 56 individuals initially randomized could be evaluated for



**Fig. 2** (Nussenblatt and associates). Average visual acuities of both eyes ( $n = 50$ ) at three months after the initiation of therapy (Course A) compared with baseline visual acuity. All visual acuities that appear above the diagonal line indicate an improvement in visual acuity with therapy.

**TABLE 2**  
STATISTICAL EVALUATION OF COURSE A RESULTS

VARIABLE	CYCLOSPORINE (N = 28)		PREDNISOLONE (N = 28)		95% CONFIDENCE INTERVAL*
	NO. SUCCESS/TOTAL	PROBABILITY OF SUCCESS	NO. SUCCESS/TOTAL	PROBABILITY OF SUCCESS	
Visual acuity (≥ 15 letters)	12/28	.429	11/28	.393	-0.22 to +0.29
Vitreous haze (≥ 2 increments)	5/15	.333	6/13	.462	-0.49 to +0.23
Combined visual acuity/vitreous haze	13/28	.464	13/28	.464	-0.26 to +0.26

\*For difference in success probabilities.

success or failure. According to the visual acuity criteria for therapeutic success (improvement of 15 letters or more from baseline value in at least one eye), 43% of the cyclosporine-treated patients were deemed therapeutic successes, whereas only 39% of the prednisolone-treated patients were considered therapeutic successes. This difference was not statistically significantly different. Consistent with the 95% confidence intervals for the true difference between success probabilities for the two groups, prednisolone could possibly be 22% more effective than cyclosporine, and cyclosporine could be 29% more effective than prednisolone. In the evaluation of patients with vitreous haze, those with 1+ or more haze at the start of the course were included. About one third of the cyclosporine-treated patients met the criteria of success, whereas almost one half of the prednisolone-treated patients did. Because of the relatively small numbers, this difference was not statistically significantly different, and the confidence limits were fairly wide. Combining the major criteria of visual acuity and vitreous

haze, 13 of 28 (46%) of the cyclosporine treated group and 13 of 28 (46%) of the prednisolone-treated group were considered therapeutic successes at the end of Course A.

Seventeen patients receiving prednisolone therapy as their initial course of therapy (Course A) were crossed over to cyclosporine therapy for their Course B therapy, whereas 13 of the cyclosporine Course A patients crossed over to the prednisolone regimen (Table 3). A 15-letter improvement in visual acuity and a meeting of the criteria for therapeutic success were seen in four patients, whereas none of the ten patients with 1+ or more haze at the initiation of Course B met the criterion of two-increment improvement in the degree of vitreous haze. It was also notable that the visual acuities of two of the 14 patients whose Course B therapies failed were observed to have improved markedly when cyclosporine and prednisolone were administered in combination at lower dosages in Course C (Table 4) than those given in either Course A or B. Although the number of patients was small, three of the five

**TABLE 3**  
STATISTICAL EVALUATION OF COURSE B RESULTS

VARIABLE	CYCLOSPORINE (N = 17)		PREDNISOLONE (N = 28)		95% CONFIDENCE INTERVAL*
	NO. SUCCESS/TOTAL	PROBABILITY OF SUCCESS	NO. SUCCESS/TOTAL	PROBABILITY OF SUCCESS	
Visual acuity (≥ 15 letters)	2/17	.118	2/13	.154	-0.29 to +0.21
Vitreous haze (≥ 2 increments)	0/5	.000	0/5	.000	—

\*For difference in success probabilities.



**TABLE 4**  
STATISTICAL EVALUATION OF COURSE C RESULTS  
[CYCLOSPORINE AND PREDNISOLONE, N = 14]

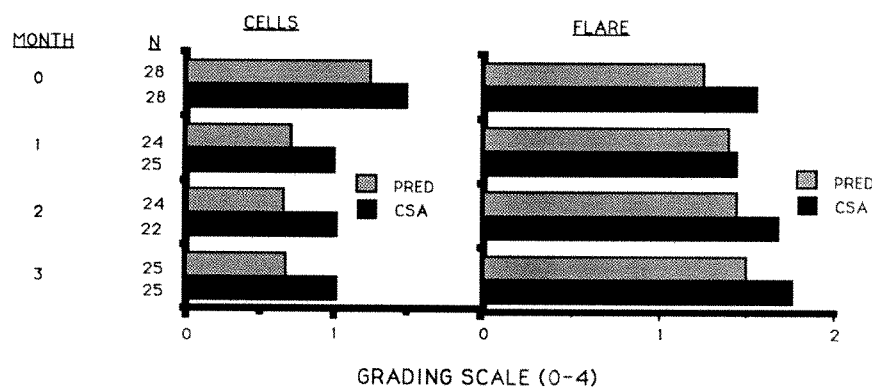
VARIABLE	SUCCESS/TOTAL
Visual acuity ( $\geq 15$ letters)	2/14 (14%)
Anterior chamber	
Cells	2/4 (50%)
Flare	2/12 (17%)
Vitreous cells	3/13 (23%)
Haze ( $\geq 2$ increments)	3/5 (60%)

patients who reached this course with a vitreal haze reading of 1+ or more had a markedly positive therapeutic response with this regimen.

Anterior chamber inflammatory values as a result of the two forms of therapy may be compared (Fig. 3). Both therapies had a positive therapeutic response on the number of inflammatory cells in the anterior chamber, although the prednisolone-treated eyes had a somewhat greater decrease in that number than did the cyclosporine-treated group at the three-month interval. Neither therapy had a marked effect on the flare. Indeed, there was a slight increase in the flare observed in both groups at three months as compared to baseline value, underscoring the fact that anterior chamber flare alone is not an indicator of active inflammatory disease. These findings are in contradistinction to those seen in the vitreal cavity. In the vitreous humor (Fig. 4), although there was an improvement in the clinical appearance of most of the eyes treated, the number of vitreal cells dropped slightly, but ultimately remained fairly stable. Generally, the vitreal haze decreased in both groups, staying that way for the 12-month follow-up period for both groups. The

response of eyes with cystoid macular edema to these therapies (Table 5) was remarkable as well. In Course A, seven of 15 (47%) of the cyclosporine-treated eyes and ten of 16 (63%) of the prednisolone-treated eyes demonstrated resolution of macular edema after three months of therapy. Using a chi-square cross tabulation, the differences observed were not statistically significantly different ( $P = .376$ ). Also of interest is that some eyes that crossed to the alternative therapy in Course B had resolution of the condition, and additional eyes that failed both Courses A and B had resolution of the macular edema when the two therapies were combined.

Secondary effects of both drugs were monitored closely. When a two-unit increase in vitreal haze was used as criterion, relatively few patients (five of 56 [four in the cyclosporine-treated group and one in the prednisolone-treated group]) had an increase in clinical appearance of cataract during the Course A period of the study. A detailed reporting system was devised for the recording of systemic adverse reactions (Table 6). Generally, patients treated with cyclosporine complained of more problems, but most problems disappeared with time or with a decrease in dosage. This was less likely to occur in the prednisolone-treated group. The two major secondary effects observed in the cyclosporine group were those of hypertension and alterations in the serum creatinine concentration, two well-known complications of cyclosporine therapy.<sup>8</sup> Although the mean systolic and diastolic blood pressures for the cyclosporine- and prednisolone-treated groups were the same at baseline, an increase in both of these values was clearly observed in the cyclosporine-treated alternative of Course A (Fig. 5). Further, an increase in serum creatinine concentration was also observed in the



**Fig. 3** (Nussenblatt and associates). Response to therapy of cell and flare in the anterior chamber. Comparison of cyclosporine- and prednisolone-treated patients.

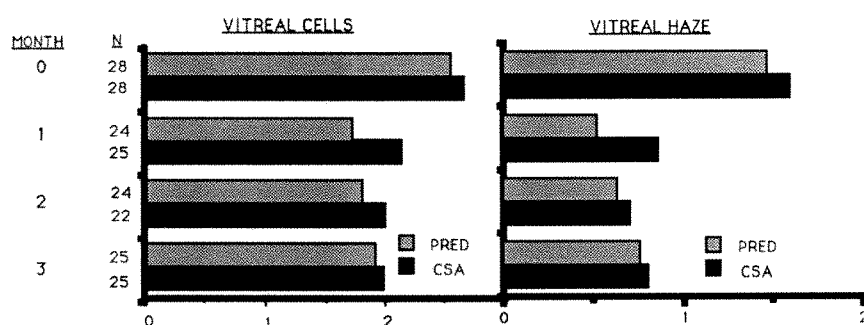


Fig. 4 (Nussenblatt and associates). Response to treatment of vitreous cells and haze. Comparison of cyclosporine- and prednisolone-treated patients.

cyclosporine-treated group, whereas the serum creatinine determinations in the prednisolone group remained unchanged (Fig. 6).

### Discussion

The two therapeutic alternatives consisted of single therapies, therefore permitting us to obtain reliable efficacy rates for both drugs, giving us for the first time data not only for cyclosporine but for a systemically given corticosteroid as well. It was also a study in which diseases that are commonly encountered in the American patient were treated with a therapeutic strategy that permitted a tailoring of the treatment regimen in a way one would normally do for these cases. To complement our observations, there have been reports concerning randomized clinical trials evaluating the effectiveness of cyclosporine in the treatment of Behçet's disease,<sup>8,9</sup> and one placebo/cyclosporine trial in the Netherlands, in which uveitis patients received predetermined decreasing dosages.<sup>12</sup>

The information gathered in this study demonstrated clearly that an improvement of visual acuity could be obtained for the vast majority of

eyes studied using either of the therapeutic alternatives (Fig. 3). When more stringent criteria are applied, that is, an improvement of visual acuity of 15 letters (three lines) or more in at least one eye, or an improvement of at least two increments on the vitreal haze scoring scheme, a smaller but essentially equal number of patients from each group was deemed a therapeutic success. Both were effective, however, in less than half of the cases treated. An additional category in which there were similar therapeutic responses was in the resolution of cystoid macular edema, in which both drugs

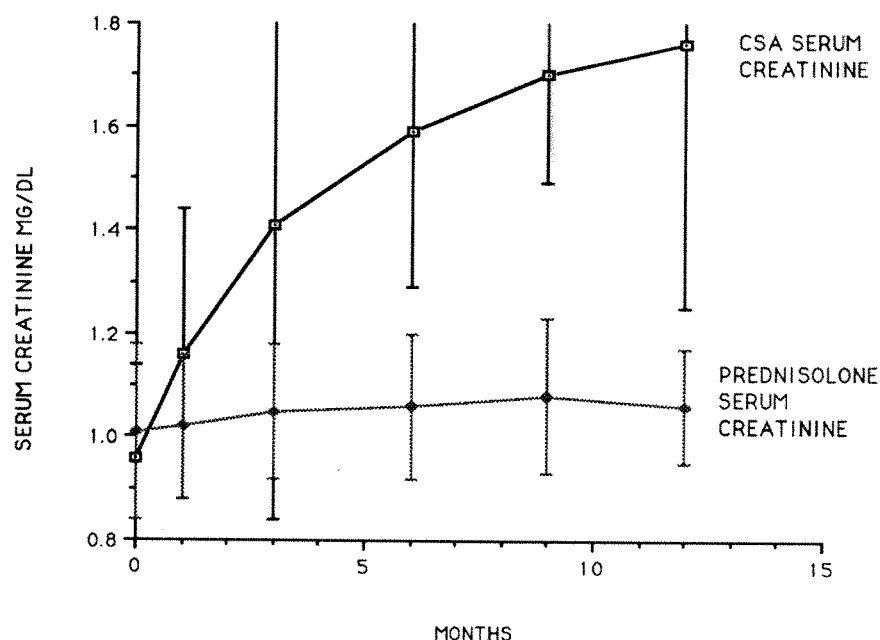
TABLE 6  
SIDE EFFECTS OF CYCLOSPORINE OR  
PREDNISOLONE AS FIRST TREATMENTS (N = 56)

SIDE EFFECT	CYCLOSPORINE (%)	PREDNISOLONE (%)
Hyperesthesia/paresthesia	96	62
Weakness	96	62
Nausea/appetite decrease	89	38
Headache	89	72
Hypertrichosis	78	45
Gastrointestinal disorders	70	59
Gingival hyperplasia	67	34
Weight gain	56	66
Breast tenderness	52	41
Tremor	48	21
Excitability	44	48
Fluid retention	41	59
Difficulty walking	37	24
Weight loss	37	14
Appetite increase	30	66
Hair loss	15	24
Muscle cramps	15	14
Acne	11	10
Diarrhea	10	14

TABLE 5  
EFFECTS OF CYCLOSPORINE OR PREDNISOLONE  
THERAPY ON CYSTOID MACULAR EDEMA AT THREE  
MONTHS

THERAPY	COURSE A (IMPROVED/ TOTAL)	COURSE B (IMPROVED/ TOTAL)	COURSE C (IMPROVED/ TOTAL)
Cyclosporine	7/15	2/8	—
Prednisolone	10/16	3/8	—
Cyclosporine and prednisolone	—	—	3/8





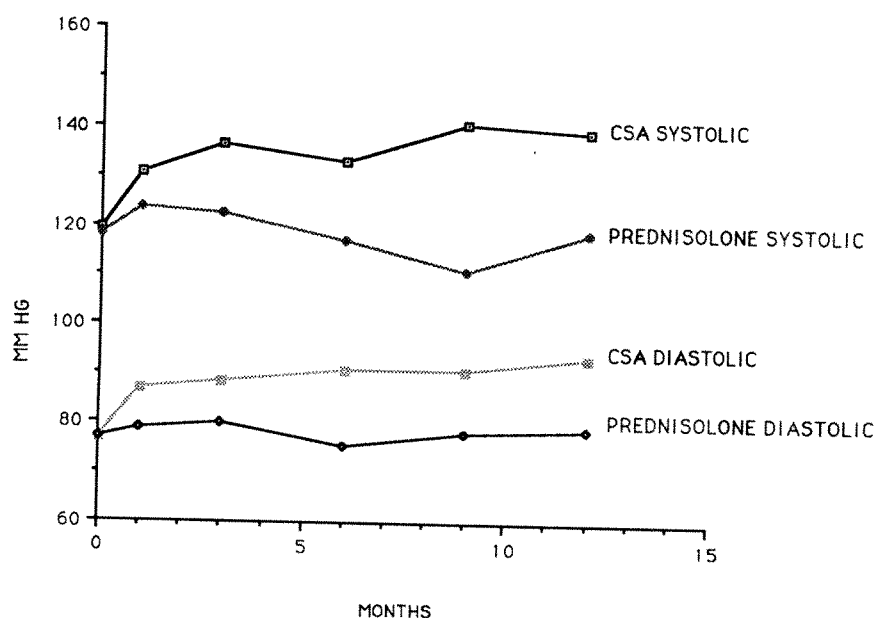
**Fig. 5** (Nussenblatt and associates). Comparison of blood pressure readings in patients receiving cyclosporine or prednisolone as a first treatment (Course A).

resulted in the improvement of this problem in less than half the cases.

Indeed, it is striking how similar the improvement rates were for both treatment alternatives for all the criteria measured. Of interest was the diminution of vitreal haze observed in both groups. Previous observations supported our choice of this value as the main endpoint in addition to visual acuity because we were able to use standardized controls and thereby de-

crease intraobserver variations.<sup>11</sup> To date, vitreal cellularity has eluded a reliable standardization system. Further, we have observed that vitreal haze disappears more rapidly than do vitreal cells. We would conjecture that the haze is a result of a release of cytokines induced by immunoreactive cells recruited into the eye. Cells, though inactive, appear to stay in the vitreous humor for a longer period of time.

Because of a change in the therapeutic dosage



**Fig. 6** (Nussenblatt and associates). Comparison of serum creatinine concentrations in patients receiving cyclosporine or prednisolone as a first treatment (Course A).

indications for cyclosporine,<sup>8</sup> the number of patients enrolled in this study could not lead to an absolute conclusion that there is no difference in the treatment effects of the two medications. Rather there may be a potential of a 20% to 30% difference in clinical efficacy between the two drugs. This observation, however, still suggests that these alternatives are therapeutic modes that can be considered for the same indications. The fact that the currently suggested starting dosage of cyclosporine is from 5 to 7.5 mg/kg of body weight/day<sup>8</sup> brings into question whether the success rates with this agent would be different than reported here. Information to date would suggest that this is not the case, and that it is the rapidity of the response, rather than the efficacy that is affected. In a recent report by Towler and associates,<sup>13</sup> a low dosage of cyclosporine was used in chronic posterior uveitis patients and this therapeutic approach achieved a sustained visual improvement in seven of nine patients. These observations reflect our long-term experience as well.

The study design provided useful information concerning each drug as an individual medical therapeutic approach, but the cross-over design added certain clinically relevant information as well. The results demonstrated that it is logical to switch to the alternative medication used in this study because some eyes appeared to benefit clinically from such a decision. Of interest were the Course C patients who received both drugs, but at lower dosage than that given in Courses A and B. Some eye therapies in these patients were ultimately felt to be clinical successes despite failure on Courses A and B. This finding underscores the potential corticosteroid-sparing effect of cyclosporine. With lower dosages of both drugs being given, combined long-term use with a decreased number of side effects is a possibility. The Course C approach reflects the current thinking concerning the use of cyclosporine in the treatment of uveitis.<sup>8</sup> Combining the relatively low starting dosage of cyclosporine (5 mg/kg of body weight/day) with a relatively low dosage of prednisone (10 to 20 mg/day) appears to diminish markedly the appearance of renal toxicity at two years,<sup>14,15</sup> a time point at which we observed marked renal changes in patients who started cyclosporine at 10 mg/day.<sup>16</sup>

Systemic corticosteroid therapy should be considered the preferred treatment in the vast majority of severe, bilateral sight-threatening

noninfectious intraocular inflammatory conditions. This would seem justified for several reasons, including the greater general experience with this drug, detailed knowledge of its long-term complications, rapidity of action, and cost. However, this study does underscore our difficulty in achieving a good clinical success with this mode of therapy. Our observations help to establish cyclosporine therapy as a logical possible alternative to prednisone therapy for severe sight-threatening uveitis in selected patients who are unable to continue systemic corticosteroid therapy. As with corticosteroid therapy, long-term cyclosporine therapy carries risks as well, particularly that of nephrotoxicity, requiring close monitoring of the patient. In some cases, the secondary side effects of both drugs could have an important role in the decision-making process for the patient. For example, in a patient with renal disease, cyclosporine therapy probably should not be considered, but in the patient who is diabetic, or who has severe mood swings when treated systemically with corticosteroids, cyclosporine might be considered. It is hoped that this study will create a precedent for similar randomized studies in this subspecialty of ophthalmology that needs to progress beyond anecdotal reports.

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#### OPHTHALMIC MINIATURE

He let his horse roam with the others in a fenced field and found himself a grassy place under a charming tree and lay flat on his back, gazing up serenely into the blue, watching those curious flecks that you can see if you stare upward against the vacant blue, the defects of your own eye.

Michael Shaara, *The Killer Angels*  
New York, Ballantine Books, 1974, p. 168

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# Analysis of Local Antibody Production in the Vitreous Humor of Patients With Severe Uveitis

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and Jan C. van Meurs, M.D.

We analyzed the local antibody production in vitreous humor samples collected during vitrectomy in patients with severe vision-threatening uveitis. In 24 patients, paired serum and undiluted vitreous humor samples were collected and tested for antibodies against *Toxoplasma gondii*, herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and *Toxocara canis*. Total IgG and the Goldmann-Witmer coefficient were determined. The initial diagnosis of ocular toxoplasmosis could be confirmed in six of the seven patients. The seventh patient showed a local antibody production against herpes simplex virus. One of the three patients with chronic panuveitis at initial diagnosis showed a local antibody production against *T. gondii*. These last two findings resulted in a change in medical treatment. Analysis of local antibody production in vitreous humor samples is a valuable diagnostic tool.

**D**ESPITE EXTENSIVE CLINICAL and laboratory tests, the cause of uveitis remains obscure in approximately 40% of the patients visiting a uveitis clinic. Only a limited amount of laboratory tests are currently useful to the ophthalmologist in the examination of patients with uveitis.<sup>1</sup> In cases of severe uveitis in which clinical examination and laboratory testing have not provided any answers concerning the cause, the assessment of local intraocular antibody production may be useful.<sup>2,3</sup> Aqueous humor analysis is now used in cases of severe

uveitis in various European ophthalmology clinics. Analysis of vitreous humor samples for local intraocular antibody production, however, has not been widely reported. Since the report of Diamond and Kaplan<sup>4</sup> on the results of vitrectomy in patients with uveitis, more authors<sup>5,6</sup> reported favorable results of vitrectomy in patients with uveitis. Only a few of these articles report on the possibility of assessment of specific antibodies in the vitreous humor,<sup>7-9</sup> although the cause in these serious cases is often enigmatic.

The measurement of antibodies in the vitreous humor can be useful as a diagnostic tool. It may influence treatment measures in patients with serious uveitis, which may be important because treatment is often time-consuming and toxic.

We studied the results of analysis of the vitreous humor samples collected during vitrectomy in 24 patients with uveitis.

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## Patients and Methods

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Paired serum and vitreous humor samples were obtained during pars plana vitrectomy performed in 24 patients with serious vision-threatening uveitis of various causes. The samples were collected undiluted, before the infusion line was opened. Vitrectomy was performed because of visual deterioration or progressive inflammation, despite aggressive medical treatment. The initial diagnoses were ocular toxoplasmosis in seven, intermediate uveitis in six, ocular toxocariasis in four, chronic panuveitis in three, acute retinal necrosis in one, cytomegalovirus retinitis in one, ocular sarcoidosis in one, and juvenile chronic arthritis in one.

Part of the vitreous humor sample of all these patients was used for the detection of antibodies. In two patients in whom a masquerade

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syndrome was possible, part of the vitreous humor sample was sent to the Department of Pathology. In three cases a portion of the vitreous humor was sent to the Department of Virology. On the day of vitrectomy, we also obtained a blood sample (10 ml) from the patient.

Both vitreous humor and serum samples were tested for antibodies against the following microorganisms (using an immunofluorescence test as described earlier): *Toxoplasma gondii*, herpes simplex virus, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus.<sup>3</sup> Antibodies against *Toxocara canis* were tested in four patients using an enzyme-linked immunosorbent assay. Immunoglobulin G and albumin concentrations were measured by radial immunodiffusion.<sup>3</sup>

The quotient of the relative amount of antibodies against the various microorganisms in the vitreous humor and serum (Goldmann-Witmer coefficient) was calculated as follows:

$$\frac{\text{antibody titer, vitreous humor}}{\text{total immunoglobulin, vitreous humor}} : \frac{\text{antibody titer, serum}}{\text{total immunoglobulin, serum}}$$

Theoretically, a coefficient above 1.0 would indicate a local production of antibodies within the eye. In view of the variability in the results of the measurements, an antibody coefficient above 3.0 was considered a positive test result.

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## Results

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Examination of the vitreous humor of two patients with possible masquerade syndrome in the Department of Pathology did not disclose any sign of a reticulum cell sarcoma. In the vitreous humor of three patients suspected to have viral retinitis, no organisms could be cultivated. The initial diagnosis could be confirmed by vitreous humor antibody analysis in six of the seven cases of ocular toxoplasmosis. In four of these patients, the antibody titer in the vitreous humor was even higher than that in the serum (Table).

The seventh patient showed an unexpected local intraocular production of antibodies against herpes simplex virus (Goldmann-Witmer coefficient, 21). The titer of antibodies against herpes simplex virus in the vitreous

humor (1:2,048) was even higher than that in the serum (1:512). This finding resulted in a drastic change in treatment. As this patient (Case 6, Table) clearly demonstrates the value of vitreous humor analysis in severe uveitis, we describe the history in some detail.

A 41-year-old man had a history of focal choroiditis in 1969 and a recurrent anterior uveitis of his left eye. In June 1990, he complained of pain in his left eye. Episcleritis was noted at initial examination, and vitreitis with a vague white lesion in the periphery of the fundus of the left eye was noted a few days later. At referral, he had a visual acuity of hand motions in his left eye, some cells in the anterior chamber, and fine keratic precipitates. Because of the extensive vitreous humor opacities, the fundus could not be seen. Echography showed no retinal detachment. With an initial diagnosis of ocular toxoplasmosis, a pars plana vitrectomy was performed and an undiluted vitreous humor sample was collected. In the vitreous humor, a local antibody production against *T. gondii* was not detected, but a local antibody production against herpes simplex virus was. The treatment was changed from administration of clindamycin and sulfonamides to infusion with acyclovir.

One of the three patients with an initial diagnosis of chronic panuveitis showed a local production of antibodies against *T. gondii* (coefficient, 5.3), with an antibody titer in the vitreous humor higher than that in the serum.

In one patient with typical clinical findings of acute retinal necrosis syndrome (Case 21, Table), we could not find a local production of antibodies in the vitreous humor against our panel of microorganisms.

Negative results were also obtained in one patient with acquired immunodeficiency syndrome and the clinical findings of cytomegalovirus retinitis. But this patient had already received treatment (DHPG) for three weeks.

Albumin concentration was measured in the vitreous humor to investigate the degree of blood-aqueous barrier breakdown. Some of the vitreous humor samples contained over 50% of serum albumin values, indicating extreme blood-aqueous barrier breakdown (Table).

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## Discussion

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Diagnoses of uveitis are largely presumptive, lacking biopsy and histologic examination of

TABLE  
ANTIBODY TITERS AND GOLDMANN—WITMER COEFFICIENT IN THE VITREOUS HUMOR OF PATIENTS WITH UVEITIS\*

PATIENT NO.	INITIAL DIAGNOSIS	IgG		ALBUMIN CONCENTRATION,		GOLDMANN-WITMER COEFFICIENT				
		VITREOUS HUMOR (MG/ML)	SERUM (MG/ML)	VITREOUS HUMOR (MG/ML)	ALBUMIN CONCENTRATION SERUM (MG/ML)	TOXO-PLASMOSIS	HERPES SIMPLEX VIRUS	CYTO-MEGALO-VIRUS	EPSTEIN-BARR VIRUS	VARICELLA-ZOSTER VIRUS
1	Ocular toxoplasmosis	5.4	12.2	16.6	30.0	9	<1	<1	<1	<1
2	Ocular toxoplasmosis	0.55	13.6	2.6	49.8	12	1.5	<1	<1	<1
3	Ocular toxoplasmosis	1.38	12.0	1.2	54.2	4.4	<1	<1	<1	<1
4	Ocular toxoplasmosis	3.1	10.0	5.4	49.4	10	1.6	<1	<1	<1
5	Ocular toxoplasmosis	2.2	5.8	21.2	41.2	10	<1	<1	<1	1.3
6	Ocular toxoplasmosis	1.4	7.3	4.6	46.8	<1	21	<1	1.3	2.6
7	Ocular toxoplasmosis	0.47	17.0	3.4	52.1	4.5	<1	<1	<1	<1
8	Intermediate uveitis	1.9	9.0	20.0	46.0	<1	<1	<1	<1	<1
9	Intermediate uveitis	0.75	9.6	5.2	46.4	<1	<1	<1	<1	1.6
10	Intermediate uveitis	0.06	11.7	0.4	47.2	<1	<1	<1	<1	<1
11	Intermediate uveitis	<0.01	10.9	<0.1	42.0	<1	<1	<1	<1	<1
12	Intermediate uveitis	0.06	15.5	0.3	49.8	<1	<1	<1	<1	<1
13	Intermediate uveitis	0.08	7.7	1.6	48.0	<1	<1	<1	<1	<1
14	Ocular toxocariasis	1.8	9.9	14.8	58.8	1.4	<1	<1	<1	<1
15	Ocular toxocariasis	2.7	9.6	17.5	49.4	<1	N.D.	N.D.	N.D.	N.D.
16	Ocular toxocariasis	5.2	12.2	24.3	37.6	<1	<1	<1	<1	<1
17	Ocular toxocariasis	0.1	14.6	1.0	50.6	<1	2.3	<1	<1	<1
18	Chronic panuveitis	0.17	8.8	0.1	41.3	<1	<1	<1	<1	<1
19	Chronic panuveitis	4.0	10.6	1.5	50.9	5.3	<1	<1	<1	<1
20	Chronic panuveitis	0.49	9.8	1.4	48.6	<1	<1	<1	<1	<1
21	Acute retinal necrosis syndrome	4.2	11.6	46.4	53.4	<1	<1	<1	<1	<1
22	Cytomegalovirus retinitis	1.6	22.5	2.0	31.4	1.1	<1	0.9	1.8	<1
23	Ocular sarcoidosis	0.1	13.2	0.3	44.3	<1	<1	<1	<1	<1
24	Juvenile chronic arthritis	9.0	13.6	30.0	66.0	<1	<1	<1	<1	<1

\*ND indicates not done.

the involved ocular structures. The diagnosis is usually made using clinical history and appearance. Serum biochemical analysis is often of little help. However, the assessment of local antibody production in the anterior chamber can give more information on the cause of inflammation.<sup>2</sup>

An even better method might be a technique involving endorectal biopsy,<sup>10</sup> but this technique has important additional risks, especially if the retina is still attached.

The results described in this study show that analysis of immunoglobulins in vitrectomy samples can be useful to the ophthalmologist in making a precise diagnosis and providing the rationale for choosing the appropriate treatment.

The protozoan parasite *T. gondii* is considered the most frequent cause of posterior uvei-

tis in Europe. In these cases, the diagnosis is usually made on the basis of the typical clinical appearance of the focal retinochoroiditis lesion. In severe cases, vitreous humor opacities may obstruct a good view of the fundus; ocular toxoplasmosis is presumptively diagnosed and antiparasitic treatment is started.

In one such patient with extensive vitreous humor opacities, vitrectomy was performed; analyzing the vitreous humor sample, we could not confirm the initial diagnosis. Instead, this patient showed a high intraocular production of antibodies against the herpes simplex virus. The fundus appearance throughout and after vitrectomy did not show the typical focal lesion as in ocular toxoplasmosis, but showed instead a more extensive lesion in the periphery of the fundus with retinal necrosis and neovascularization.



The initial diagnosis of *Toxoplasma* retinochoroiditis was generally confirmed by analysis of intraocular antibodies. Of interest was the observation that values of *Toxoplasma* antibodies in the vitreous humor were even higher than those in the peripheral blood. The most obvious explanation for this finding is that intraocular plasma cells produce these antibodies. The exact location of these plasma cells is not yet certain, but it seems likely that they exist in the posterior segment of the eye, possibly adjacent to the chorioretinal lesions.

Aqueous humor analysis in patients with ocular toxoplasmosis has also indicated a local intraocular antibody production in these eyes, but until now aqueous humor antibody values have not exceeded those detected in the blood.

The observation of vitreous humor antibody values exceeding serum biochemical values would have been missed if we had used diluted vitrectomy samples. Dilution of vitrectomy samples masks the measurement of the exact antibody value in the vitreous humor. As yet, no markers are available to detect the dilution factor of the vitreous humor. Obtaining a large enough volume of undiluted vitreous humor samples is not always easy and not always without hazards. However, as we have seen, it is important to try to obtain undiluted vitreous humor samples for analysis. For the examination of cells in the vitreous humor, it may even be essential.

Immunoglobulins in the vitreous humor can be caused by either blood-retinal barrier breakdown, intraocular antibody production, or a combination of both.

Blood-retinal barrier breakdown can be calculated by measuring the vitreous concentration of a serum protein in the blood that is not being produced by ocular structures. We, therefore, also measured albumin concentrations in both the vitreous humor and serum samples and calculated an antibody coefficient using the albumin values. This did not result in a more accurate determination of local antibody synthesis, but did indicate that some Goldmann-Witmer coefficients could have been negative because of extreme blood-aqueous barrier breakdown.

It is likely that the amount of different microorganisms to which local intraocular antibody

production can be detected will increase in the near future.

Because the choice of the often aggressive medical treatment, particularly in infectious uveitis entities, depends directly on the causative organism, it is of the utmost importance to confirm an uncertain clinical diagnosis with a tailored analysis of vitrectomy samples.

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# Clinical Patterns and Associated Conditions in Chronic Uveitis

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We determined the relative frequencies of the different types of chronic uveitis, and the possible associated conditions, among 400 consecutive patients with chronic uveitis examined during the years 1982 through 1988. Of the 400 patients, 183 (45.75%) had anterior uveitis, 98 (24.5%) had panuveitis, 61 (15.3%) had intermediate uveitis, and 58 (14.5%) had isolated posterior uveitis. Only four of the 98 patients with panuveitis (4.1%) were considered idiopathic after a comprehensive examination, whereas 94 of the 183 patients with anterior uveitis (51.4%) were similarly classified. We found an associated condition in 242 of the 400 patients of the study group (60.5%). Of these 242 patients, 61 had Behçet's disease, which constituted the most frequently encountered associated condition in this study. Of the 61 patients with Behçet's disease, 58 had panuveitis and constituted 59.2% of the panuveitis group. Of the 61 patients with intermediate uveitis, 17 (27.9%) had a concurrent disease. An associated condition was found in 95% and 96.2% of patients with unilateral and bilateral panuveitis, respectively, but in none of the patients with unilateral intermediate uveitis. Environmental, cultural, or genetic factors may be accountable for the differences discovered between our findings and those of previously published studies from the United States and England with respect to relative frequencies of some of the associated diseases in patients with chronic uveitis.

**C**HRONIC UVEITIS is a nonspecific clinical manifestation triggered by various factors, probably

regulated by the state of the host immune system,<sup>1-4</sup> and possibly results in severe complications. In view of the nonspecific nature of the uveitic process, examining the patients for associated conditions that may be involved in the pathogenesis of chronic uveitis could contribute to the understanding and treatment of the disease.

In this study, the extent of ocular involvement, the associated conditions, and the likelihood to detect a concurrent disease in different subgroups of patients were analyzed in 400 patients with chronic uveitis. To try to determine whether environmental, cultural, or genetic factors could have a bearing on the results, we also compared our results with those previously reported from some other uveitis centers in the United States and England.

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## Subjects and Methods

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We evaluated the records of 400 consecutive patients (6 to 75 years old) with chronic uveitis examined during the years 1982 through 1988. Chronic uveitis was diagnosed when intraocular inflammatory clinical signs persisted for three months or longer. Most of the patients studied had chronic uveitis for a duration of six months to 15 years. All patients were referred to the Uveitis Service of the Hadassah Medical Center of the Hebrew University. We reviewed the history, clinical findings, and laboratory data of these patients to verify the type of chronic uveitis, and possibly to confirm the presence of an associated disease.

On the basis of the ocular structures predominantly affected by the uveitic process, the 400 patients were subclassified into the four following groups: (1) anterior uveitis group, patients with iritis or iridocyclitis characterized by flare and cells in the anterior chamber without manifest involvement of the vitreous; (2) intermediate uveitis group, patients with inflammation predominantly involving the pars plana region;

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(3) isolated posterior uveitis group, patients with choroiditis or chorioretinitis with mild to moderate cellular infiltration confined to the posterior vitreous; and (4) panuveitis group, patients with inflammatory findings in both the anterior and posterior segments with marked cellular infiltration of the vitreous humor.

The 400 cases were also divided into eight subgroups on the basis of the type of chronic uveitis (anterior, intermediate, isolated posterior, or panuveitis) and whether the condition was unilateral or bilateral. We assessed the likelihood to detect a coexisting disease in each of these subgroups.

Laboratory examination in each case included a complete blood cell count with a differential, erythrocyte sedimentation rate, serum biochemical analysis (for example, glucose, urea, creatinine, and bilirubin concentrations, and serum levels of liver enzymes), the Venereal Disease Research Laboratory test, serologic tests for toxoplasma, toxocara, cytomegalovirus, herpes simplex and zoster, Epstein-Barr, rubella, and the immunodeficiency syndrome viruses, human lymphocyte antigen typing, urinalysis for sediments and electrolytes, skin tuberculin test, and thoracic radiography. Additional tests, performed when specifically indicated, included fluorescein angiography, anterior chamber or vitreous tap, cranial imaging, liver and spleen scan, and kidney biopsy.

The definitions and the basis for the diagnosis of some of the associated noninfectious conditions found among patients in this study are the following: Behçet's disease; recurrent oral and genital aphthous ulcerations; juvenile rheumatoid arthritis; objective arthritis of six weeks' or more duration beginning before age 17 years; systemic lupus erythematosus; some combination of clinical findings such as arthropathy (usually arthritis), myopathy, malar rash and other skin lesions, nephritis, vasculitis, and central nervous system abnormalities, with the demonstration of serum antinuclear antibodies (particularly anti-double-stranded DNA and anti-small nuclear ribonucleoprotein antibodies). Some additional definitions and bases for diagnosis of associated noninfectious conditions are the following: Reiter's syndrome; reactive arthritis after a urogenital infection, usually with a positive human lymphocyte antigen B27 typing; sarcoidosis; some combination of findings such as interstitial lung disease, bilateral hilar adenopathy and other lymphadenopathy, and skin abnormalities,

with an increased serum level of angiotensin-converting enzyme and the demonstration of a noncaseating granulomatous process by lung parenchyma or other tissue biopsy; Vogt-Koyanagi-Harada syndrome; uveitis associated with findings such as dysacusis, alopecia, and vitiligo; sympathetic ophthalmia, the appearance of inflammation in the sympathizing eye after surgery or injury to the fellow eye. The diagnosis of associated infectious conditions in patients of this study was confirmed by one or more of the following: detection of high levels ( $\geq 1:1,024$ ) of specific serum antibodies (toxoplasmosis); a fourfold or greater change in specific serum antibody titer (for example, toxoplasmosis, adenovirus, herpes simplex, herpes zoster) demonstrated by two blood samples taken four weeks apart; an increased ratio of aqueous humor to serum-specific antibody titer (for example, toxoplasmosis and herpes simplex); and cultures of specimens taken from the base of corneal ulcers (herpes simplex), vesicular fluid (herpes zoster), or conjunctival sac (adenovirus).

## Results

Males and females (6 to 75 years old) were evenly distributed among patients with anterior, intermediate, and isolated posterior chronic uveitis, whereas 65 of the 98 patients with panuveitis (66.3%) were males (Table 1).

Anterior uveitis was the most frequently encountered type of chronic uveitis in our study (183 of the 400 patients; 45.8%). Panuveitis, intermediate uveitis, and isolated posterior uveitis were diagnosed in 98 (24.5%), 61 (15.2%), and 58 (14.5%) of the 400 patients, respectively. These findings were compared with those reported in previous studies (Table 2).<sup>5-7</sup>

TABLE 1  
GENDER DISTRIBUTION OF CHRONIC UVEITIS

CHRONIC UVEITIS TYPE	MALE		FEMALE	
	NO.	%	NO.	%
Anterior	86	47.0	97	53.0
Intermediate	32	52.5	29	47.5
Isolated posterior	33	56.9	25	43.1
Panuveitis	65	66.3	33	33.7
Behçet's disease	43	70.5	18	29.5

TABLE 2  
ANATOMIC SUBDIVISIONS IN CHRONIC UVEITIS

CHRONIC UVEITIS TYPE	DARREL AND ASSOCIATES <sup>5</sup>		PERKINS AND FOLK <sup>6</sup>		HENDERLY AND ASSOCIATES <sup>7</sup>		THIS STUDY	
	NO.	%	NO.	%	NO.	%	NO.	%
Anterior	51	54.2	104	59.8	167	27.8	183	45.8
Intermediate	—	—	11	6.3	92	15.3	61	15.2
Isolated posterior	28	29.8	41	23.6	230	38.3	58	14.5
Panuveitis	15	16.0	18	10.3	111	18.5	98	24.5
Total	94	100.0	174	100.0	600	100.0	400	100.0

Of the 400 cases, 158 (39.5%) were considered idiopathic despite an extensive clinical and laboratory evaluation (Table 3). The majority of the idiopathic cases had anterior uveitis (94 of 158 cases; 59.5%).

The different associated noninfectious conditions in this study were determined (Table 3). Behçet's disease was the most frequently diagnosed associated condition among our 400 patients (61 cases; 15.3%). Of the 61 patients with Behçet's disease, 58 (95.1%) had panuveitis. External trauma (including surgery) constituted the second most frequent concurrent condition, and all of the 32 patients with trauma had anterior uveitis. Fifteen of the 400 patients of the study group (3.8%) had sympathetic ophthalmia; of these 15 patients, nine had panuveitis, whereas the other six patients had only isolated posterior uveitis at initial examination.

The different associated infectious diseases were also determined (Table 3). Herpesvirus was the most frequently diagnosed agent; evidence for a herpetic infection was detected in 20 of the 400 patients of the study group (5.0%). Of these 20 patients, 19 were infected by the herpes simplex virus and only one patient showed evidence for herpes zoster virus infection. We diagnosed toxoplasmosis in 15 of the 400 patients of the study group (3.8%). Of these 15 patients, eight had a typical posterior pole chorioretinal lesion, whereas seven others had unilateral panuveitis without the typical lesion, and the diagnosis was established serologically. Of the seven patients with toxoplasmosis and unilateral panuveitis, three had intermediate uveitis, which later developed into panuveitis.

The various coexisting conditions among patients with anterior uveitis were determined and compared with those reported in other studies from other geographic regions (Table

4).<sup>5,7</sup> Ninety-four patients (51.4% of the anterior uveitis group) were considered idiopathic despite an extensive examination. Among the 89 patients in whom an associated condition was found, the two most common conditions were trauma (32 of the 183 cases in the anterior uveitis group [17.5%]) and herpes simplex virus infection (14 cases; 7.7%).

Among the 61 patients with intermediate uveitis, 17 (27.9%) had a coexisting disease (Table 5). *Klebsiella pneumoniae* infection (associated with a positive human lymphocyte antigen B27 typing) and adenovirus infection were diagnosed in three and five cases, respectively. Other associated conditions included leptospirosis, Crohn's disease, ulcerative colitis, juvenile rheumatoid arthritis, systemic lupus erythematosus, and interstitial nephritis. Results from two other studies were used for comparison (Table 5).<sup>6,7</sup>

The different concurrent diseases in patients with isolated posterior uveitis were determined and compared with those in three other studies (Table 6).<sup>5-7</sup> Of the 58 cases with isolated posterior uveitis, 16 (27.6%) were classified as idiopathic, eight (13.8%) had toxoplasmosis, six (10.3%) had sympathetic ophthalmia, and five (8.6%) were diagnosed with serpiginous chorioiditis.

The various coexisting conditions disclosed among patients with panuveitis are enumerated in Table 7. Only four of the 98 patients in the panuveitis group (4.1%) were considered idiopathic. We diagnosed Behçet's disease in 58 of the 98 patients with panuveitis (59.2%) and sympathetic ophthalmia in nine (9.2%). These findings were compared with those of previously published studies (Table 7).<sup>5-7</sup>

When the 400 cases were divided into eight subgroups on the basis of the type of chronic uveitis (anterior, intermediate, isolated posteri-



**TABLE 3**  
**ASSOCIATED NONINFECTIOUS AND INFECTIOUS CONDITIONS IN CHRONIC UVEITIS**

ASSOCIATED CONDITION	ANTERIOR		INTERMEDIATE		POSTERIOR*		PANUVEITIS		TOTAL	
	NO.	%†	NO.	%†	NO.	%†	NO.	%†	NO.	%†
<b>Associated Noninfectious Conditions</b>										
None (idiopathic)	94	23.5	44	11.0	16	4.0	4	1.0	158	39.5
Behçet's disease	1	0.3	—	—	2	0.5	58	14.5	61	15.3
Trauma/surgery	32	8.0	—	—	—	—	—	—	32	8.0
Sympathetic ophthalmia	—	—	—	—	6	1.5	9	2.2	15	3.7
Juvenile rheumatoid arthritis	7	1.7	1	0.3	—	—	5	1.3	13	3.3
HLA B27	9	2.3	3	0.7	—	—	—	—	12	3.0
Fuchs' heterochromic iridocyclitis	6	1.5	—	—	—	—	—	—	6	1.5
Leukemia	4	1.0	—	—	2	0.5	—	—	6	1.5
Serpiginous choroiditis	—	—	—	—	5	1.3	—	—	5	1.3
Reiter's syndrome	3	0.7	—	—	—	—	1	0.3	4	1.0
Reticulum cell sarcoma	—	—	—	—	2	0.5	2	0.5	4	1.0
Inflammatory bowel disease	1	0.3	3	0.7	—	—	—	—	4	1.0
Birdshot retinochoroidopathy	—	—	—	—	3	0.7	—	—	3	0.7
Acute posterior multifocal placoid pigment epitheliopathy	—	—	—	—	3	0.7	—	—	3	0.7
Vogt-Koyanagi-Harada syndrome	—	—	—	—	—	—	3	0.7	3	0.7
Systemic lupus erythematosus	1	0.3	1	0.2	—	—	—	—	2	0.5
Sarcoidosis	—	—	—	—	1	0.3	1	0.2	2	0.5
Interstitial nephritis	—	—	2	0.5	—	—	—	—	2	0.5
Others‡	4	1.0	—	—	—	—	1	0.2	5	1.2
<b>Associated Infectious Conditions</b>										
Herpes virus	15	3.7	—	—	3	0.7	2	0.5	20	5.0
Toxoplasmosis	—	—	—	—	8	2.0	7	1.7	15	3.8
<i>Toxocara</i> sp.	—	—	—	—	2	0.5	3	0.7	5	1.3
Adenovirus	—	—	5	1.3	—	—	—	—	5	1.3
Leprosy	2	0.5	—	—	—	—	1	0.2	3	0.7
Tuberculosis	3	0.7	—	—	—	—	—	—	3	0.7
<i>Candida albicans</i>	—	—	—	—	2	0.5	—	—	2	0.5
Congenital rubella	—	—	—	—	2	0.5	—	—	2	0.5
Leptospirosis	—	—	2	0.5	—	—	—	—	2	0.5
Others§	1	0.2	—	—	1	0.2	1	0.2	3	0.7

\*Isolated posterior uveitis.

†Percentage of total study group (400 cases).

‡Four single cases of anterior uveitis (glaucomatous cyclitic crisis, rheumatoid arthritis, paraproteinemia, and chronic granulomatous hepatitis) and one case of lens-induced panuveitis.

§Three single cases of syphilis (anterior uveitis), cytomegalovirus (isolated posterior uveitis), and brucellosis (panuveitis).

or, or panuveitis) and whether the condition was unilateral or bilateral, a difference in the likelihood to detect a concurrent disease after a comprehensive evaluation was found (Table 8). An associated condition was found in 19 of 20 patients with unilateral panuveitis (95%) and in 75 of 78 patients with bilateral panuveitis (96.2%), but in none of the 16 patients with unilateral intermediate uveitis.

## Discussion

Our findings were comparable to those of previously published studies from the United States and England<sup>5-7</sup> with respect to the relative frequencies of the four types of chronic uveitis (anterior, intermediate, isolated posterior, and panuveitis) and the relative frequency

TABLE 4  
ASSOCIATED CONDITIONS IN ANTERIOR UVEITIS

ASSOCIATED CONDITION	ENGLAND (1961) <sup>5</sup>		U.S.A. (1984) <sup>6</sup>		U.S.A. (1986) <sup>7</sup>		ISRAEL (1988)	
	NO.	%*	NO.	%*	NO.	%*	NO.	%*
None (idiopathic)	271	44.1	58	55.7	72	43.1	94	51.4
Trauma/surgery	—	—	—	—	10	5.9	32	17.5
Herpes simplex	—	—	—	—	10	5.9	14	7.7
Juvenile rheumatoid arthritis	1	0.2	9	8.8	17	10.2	7	3.8
Fuchs' heterochromic iridocyclitis	30	4.9	11	10.5	11	6.6	6	3.3
HLA B27 with ankylosing spondylitis	97	15.8	10	9.5	9	5.4	5	2.7
HLA B27 without ankylosing spondylitis	—	—	—	—	18	10.8	4	2.2
Leukemia	—	—	—	—	—	—	4	2.2
Reiter's syndrome	158	25.7	9	8.8	6	3.6	3	1.6
Tuberculosis	2	0.3	—	—	—	—	3	1.6
Leprosy	—	—	—	—	—	—	2	1.1
Syphilis	—	—	—	—	5	3.0	1	0.5
Herpes zoster	—	—	—	—	5	3.0	1	0.5
Inflammatory bowel disease	—	—	4	3.8	2	1.2	1	0.5
Glaucomatocyclitic crisis	—	—	—	—	2	1.2	1	0.5
Others	55	8.9	3	2.9	—	—	5†	2.7
Total	614	100.0	104	100.0	167	100.0	183	100.0

\*Percentage in each series.

†Five single cases of Behçet's disease, rheumatoid arthritis, paraproteinemia, systemic lupus erythematosus, and chronic granulomatous hepatitis.

of the idiopathic cases among patients with anterior and isolated posterior uveitis. However, some differences were noted with respect to other findings.

We diagnosed Behçet's disease in 61 of our 400 patients (15.3% of the study group); this disease constituted the single most common associated condition found in this study. In other studies, Behçet's disease was diagnosed in only 0.1% to 4.0% of the patients.<sup>5-7</sup> This difference could probably be accounted for by the relatively high frequency of Behçet's disease in the Mediterranean basin<sup>8,9</sup> and the Hadassah Medical Center being a major referral facility for patients with Behçet's disease and severe chronic uveitis. The relatively low rate of idiopathic cases in our panuveitis group (4.1%, as compared with 27.8% to 92.0% reported by other investigators<sup>5-7</sup>) and the 2:1 male to female ratio found in the panuveitis group (not found among patients with other types of chronic uveitis) could be attributed to the relatively high frequency of Behçet's disease found among our patients with panuveitis, and the male preponderance known to exist in Behçet's disease, respectively.<sup>8-10</sup>

In addition to the number of patients with

Behçet's disease, the number of our patients with two other conditions, namely, sarcoidosis and the presumed ocular histoplasmosis syndrome, was also different when compared with

TABLE 5  
ASSOCIATED CONDITIONS IN INTERMEDIATE UVEITIS

ASSOCIATED CONDITION	ISRAEL (1988)		U.S.A. (1984) <sup>6</sup>		U.S.A. (1986) <sup>7</sup>	
	NO.	%*	NO.	%*	NO.	%*
None (idiopathic)	44	72.1	11	100.0	92	100.0
Adenovirus	5	8.3	—	—	—	—
<i>Klebsiella pneumoniae</i> with HLA B27	3	4.9	—	—	—	—
Leptospirosis	2	3.3	—	—	—	—
Crohn's disease	2	3.3	—	—	—	—
Interstitial nephritis	2	3.3	—	—	—	—
Ulcerative colitis	1	1.6	—	—	—	—
Juvenile rheumatoid arthritis	1	1.6	—	—	—	—
Systemic lupus erythematosus	1	1.6	—	—	—	—
Total	61	100.0	11	100.0	92	100.0

\*Percentage in each series.



**TABLE 6**  
ASSOCIATED CONDITIONS IN ISOLATED POSTERIOR UVEITIS

ASSOCIATED CONDITION	ENGLAND (1961) <sup>5</sup>		U.S.A. (1984) <sup>6</sup>		U.S.A. (1986) <sup>7</sup>		ISRAEL (1988)	
	NO.	%*	NO.	%*	NO.	%*	NO.	%*
None (idiopathic)	54	32.8	14	34.1	76	33.0	16	27.6
Toxoplasmosis	90	54.5	16	39.0	42	18.3	8	13.8
Sympathetic ophthalmia	—	—	—	—	—	—	6	10.3
Serpiginous choroiditis	—	—	—	—	12	5.2	5	8.6
Acute posterior multifocal placoid pigment epitheliopathy	—	—	—	—	11	4.8	3	5.2
Birdshot retinochoroidopathy	—	—	—	—	7	3.0	3	5.2
Acute retinal necrosis	—	—	—	—	8	3.5	3	5.2
Congenital rubella	—	—	—	—	—	—	2	3.4
Behçet's disease	1	0.6	7	17.1	—	—	2	3.4
<i>Toxocara</i> sp.	—	—	—	—	16	6.9	2	3.4
Reticulum cell sarcoma	—	—	—	—	7	3.0	2	3.4
<i>Candida albicans</i>	—	—	—	—	6	2.6	2	3.4
Leukemia/lymphoma	—	—	2	4.9	7	3.0	2	3.4
Cytomegalovirus	—	—	—	—	15	6.5	1	1.7
Sarcoidosis	—	—	1	2.4	—	—	1	1.7
Presumed ocular histoplasmosis	—	—	—	—	21	9.1	—	—
Others	20	12.1	1	2.4	2	0.8	—	—
Total	165	100.0	41	100.0	230	100.0	58	100.0

\*Percentage in each study group.

that reported by other investigators. Whereas we diagnosed sarcoidosis in only two patients (one with isolated posterior uveitis and one with panuveitis), patients with sarcoidosis con-

stituted 20.7% and 27.8% of the cases of panuveitis in two studies from the United States.<sup>6,7</sup> The presumed ocular histoplasmosis syndrome was previously found in 9.1% of patients with

**TABLE 7**  
ASSOCIATED CONDITIONS IN PANUVEITIS

ASSOCIATED CONDITION	ENGLAND (1961) <sup>5</sup>		U.S.A. (1984) <sup>6</sup>		U.S.A. (1986) <sup>7</sup>		ISRAEL (1988)	
	NO.	%*	NO.	%*	NO.	%*	NO.	%*
None (idiopathic)	127	92.0	5	27.8	50	45.0	4	4.1
Behçet's disease	—	—	—	—	11	9.9	58	59.2
Sympathetic ophthalmia	—	—	—	—	2	1.8	9	9.2
Toxoplasmosis	—	—	—	—	—	—	7	7.1
Juvenile rheumatoid arthritis	—	—	—	—	—	—	5	5.1
Vogt-Koyanagi-Harada syndrome	—	—	—	—	20	18.0	3	3.1
<i>Toxocara</i> sp.	—	—	5	27.8	—	—	3	3.1
Acute retinal necrosis	—	—	—	—	—	—	2	2.0
Reticulum cell sarcoma	—	—	2	11.1	—	—	2	2.0
Sarcoidosis	7	5.0	5	27.8	23	20.7	1	1.0
Reiter's syndrome	—	—	—	—	—	—	1	1.0
Leprosy	—	—	—	—	—	—	1	1.0
Brucellosis	—	—	—	—	1	0.9	1	1.0
Phacogenic	—	—	—	—	4	3.6	1	1.0
Syphilis	4	3.0	1	5.5	—	—	—	—
Total	138	100.0	18	100.0	111	100.0	98	100.0

\*Percentage in each study group.

**TABLE 8**  
THE LIKELIHOOD TO DETECT ASSOCIATED CONDITIONS IN CHRONIC UVEITIS

CHRONIC UVEITIS TYPE	TOTAL NO. OF CASES		ASSOCIATED CONDITION FOUND			
	UNILATERAL	BILATERAL	AMONG UNILATERAL CASES		AMONG BILATERAL CASES	
	NO.	NO.	NO.	%*	NO.	%*
Anterior	123	60	66	53.7	23	38.3
Intermediate	16	45	0	0.0	17	37.8
Isolated posterior	30	28	23	76.7	19	67.9
Panuveitis	20	78	19	95.0	75	96.2

\*Percentage in each subgroup (for example, percentage in unilateral anterior uveitis subgroup).

posterior uveitis,<sup>7</sup> but we did not find this disease in any of our 400 patients.

We found concurrent conditions in 17 of the 61 patients with intermediate uveitis (27.9%), whereas all of the patients with this type of chronic uveitis described by Perkins and Folk<sup>6</sup> and by Henderly and associates<sup>7</sup> were considered idiopathic. Other investigators have also found associated diseases in some of the patients with intermediate uveitis.<sup>11-19</sup>

The typical chorioretinal lesion of toxoplasmosis was detected in eight of our 58 patients with isolated posterior uveitis (13.8%). Serologic evidence helped to establish the diagnosis of toxoplasmosis in seven additional patients without the typical chorioretinal lesion. Four of them had panuveitis and three others had intermediate uveitis at initial examination that later developed into panuveitis. Three previously published studies have not reported toxoplasmosis in patients with panuveitis.<sup>5-7</sup>

Cytomegalovirus retinitis was reported to affect 6.5% of cases with isolated posterior uveitis,<sup>7</sup> but we diagnosed this condition in only one of our 400 patients. However, since the conclusion of this study in 1988, we have diagnosed this disease in four additional patients. Of these four patients, the disease was diagnosed in two after bone marrow transplantation, and the acquired immunodeficiency syndrome was subsequently diagnosed in two others. These findings may reflect an increasing use of immunomodulating treatments as well as an increasing frequency of the acquired immunodeficiency syndrome in our region.

The effort to identify an associated condition in patients with chronic uveitis usually requires a full laboratory examination, which is time-consuming and costly. Situations may develop in which financial or other constraints could force the clinician to limit the examination of an

individual patient. In such circumstances, the clinician and the patient may be encouraged to pursue further a complete examination when unilateral or bilateral panuveitis is diagnosed because, on the basis of our results, a relatively high diagnostic yield could be expected in such cases.

Associated conditions such as Behçet's disease, and particularly some concurrent infectious diseases, can possibly be considered as underlying causes in some of the cases with chronic uveitis evaluated in this study. However, this study did not investigate the mechanisms by which such conditions could induce chronic uveitis, or demonstrate a direct causative relationship between associated diseases and chronic uveitis.

The results of our study may not reflect the true incidence or prevalence of the various types of chronic uveitis in our region because the data are biased by the nature of our Uveitis Service being a referral center for cases with severe chronic uveitis. Nonetheless, when our observations are compared with those reported by uveitis centers from other geographic areas, a possible influence of environmental, cultural, or genetic factors, on the relative frequencies of associated conditions such as Behçet's disease, sarcoidosis, and the presumed ocular histoplasmosis syndrome, may be suggested.

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# An Updated Classification of Retinal Detachment With Proliferative Vitreoretinopathy

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The Retina Society classification on proliferative vitreoretinopathy of 1983 has been updated to accommodate major progress in understanding of this disease. There are three grades describing increasing severity of the disease. Posterior and anterior location of the proliferations have been emphasized. A more detailed description of posterior and anterior contractions has been made possible by adding contraction types such as focal, diffuse, subretinal, circumferential contraction, and anterior displacement. The extent of the abnormality has been detailed by using clock hours instead of quadrants.

AS PROLIFERATIVE VITREORETINOPATHY became amenable to therapy, need for a more detailed description of the various stages of the disease arose.<sup>1</sup> To meet the need, in 1983 the Retina Society proposed an internationally accepted classification.<sup>2</sup> More recently, however, major progress in the understanding of the disease and therapeutic advancements have revealed shortcomings in this classification. In 1989, results of a major randomized trial to evaluate the efficacy of silicone oil compared to pro-

longed intraocular gas tamponade, carried out at multiple centers, led investigators in that study to reclassify proliferative vitreoretinopathy.<sup>3</sup> Modifications were also proposed by other investigators.<sup>4</sup>

In response, the Retina Society appointed a committee to reevaluate the classification of proliferative vitreoretinopathy and suggest modifications if needed. The Committee was charged with finding a uniform, internationally acceptable classification to eliminate possible confusion resulting from multiple new classification attempts in the United States and elsewhere. This new uniform classification is now complete.

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## Classification

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The Retina Society classification of 1983 described proliferative vitreoretinopathy in four grades of severity: A, B, C, and D. The new classification retains Grades A and B, modifies Grade C, and eliminates Grade D.

**Grade A**—Denotes the earliest recognizable manifestation of intraocular proliferation, that is, pigment clumps resulting from multiplication of pigmented cells in the vitreous matrix. Clusters of pigmented cells may also be seen on the surface of the inferior retina. A Tyndall effect appears as the result of exudation into the vitreous cavity. The posterior vitreous surface is less mobile and better visible (Fig. 1).

**Grade B**—Defined by the presence of wrinkling of the inner retinal surface and retinal breaks with rolled or irregular edges (Fig. 2). The retina may appear rigid, and the retinal vessels may show tortuosity brought about by very thin preretinal membranes that are not visible by indirect ophthalmoscopy. Decreased mobility of the vitreous is also observed.

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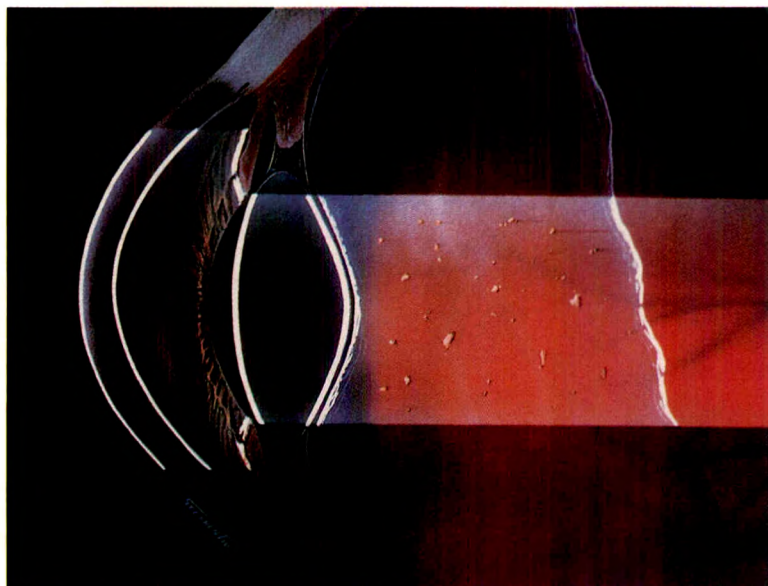
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**Fig. 1** (Machemer and associates). Proliferative vitreoretinopathy Grade A. Schematic drawing of pigmented clumps and Tyndall effect visible in vitreous with the slit lamp. The posterior vitreous surface appears condensed. (Published courtesy of Ophthalmology 90:121, 1983.)

**Grade C**—Defined by full-thickness rigid retinal folds. Grade C proliferative vitreoretinopathy is subdivided into posterior (P) and anterior (A) forms, the dividing line between the two areas being roughly the equator of the globe. The extent of the proliferation in each area is expressed by the number of clock hours of the retina involved (1–12). Frequently the proliferations are not contiguous. The vitreous is heavily condensed and contains strands.

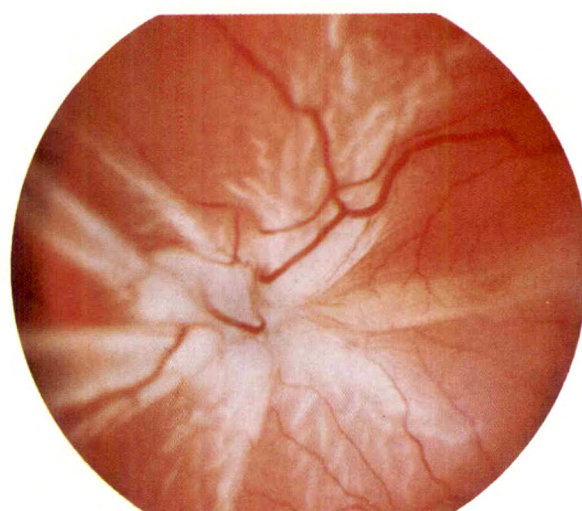
These revised grades (Table 1) give a comprehensive general picture of proliferative vitreo-

retinopathy. The Committee perceived, however, that a more detailed description of the findings was necessary. Thus Grade C is subdivided to describe the following types of contraction (Table 2). The extent of the proliferation of each type may also be expressed in the number of retinal clock hours involved.

**Type 1**—Focal posterior contraction denotes a single starfold or multiple isolated single starfolds. Localized contraction in the center of the starfold causes radiating full-thickness retinal folds in a star-shaped pattern (Fig. 3). This type occurs posterior to the vitreous base.



**Fig. 2** (Machemer and associates). Proliferative vitreoretinopathy Grade B. Irregular and partially rolled edge of retinal tear.



**Fig. 3** (Machemer and associates). Proliferative vitreoretinopathy Grade C. Type 1, focal contraction (starfold).

*Type 2*—Diffuse posterior contraction is the result of the confluence of many focal epicenters of contraction, marked by areas of irregular full-thickness retinal folding (Fig. 4). This type also occurs posterior to the vitreous base.

*Type 3*—Subretinal proliferations caused by solid strands can appear as an annular fold of the retina in the region near the optic disk, as a subretinal linear band with retina draped over it, similar to a clothesline, or when caused by membranes as irregular sheets with a moth-eaten appearance (Fig. 5). They are often pigmented but may also lack pigment.

Only if the subretinal proliferations elevate the retina or produce fixed retinal folds, which are evident by ophthalmoscopy, the extent of the proliferation is recorded. The extent of flat subretinal sheets, which are often difficult to visualize, is not recorded. Subretinal proliferations are found both posteriorly and anteriorly to the equator.

*Type 4*—Circumferential contraction is the result of diffuse membrane contraction on the retinal surface and along the juncture of the retina and the posterior surface of the detached vitreous. This is usually anterior to the equator. Contraction of preretinal tissue and across the posterior hyaloid surface produces central displacement of the retina, with stretching of the retina anterior to it as well as radial folds and a funnel formation of the retina posterior to it. Circumferential contraction can also occur after

**TABLE 1**  
PROLIFERATIVE VITREORETINOPATHY DESCRIBED BY GRADE

GRADE	FEATURES
A	Vitreous haze; vitreous pigment clumps; pigment clusters on inferior retina
B	Wrinkling of inner retinal surface; retinal stiffness; vessel tortuosity; rolled and irregular edge of retinal break; decreased mobility of vitreous
C P 1-12	Posterior to equator: focal, diffuse, or circumferential full-thickness folds*; subretinal strands*
C A 1-12	Anterior to equator: focal, diffuse, or circumferential full-thickness folds*; subretinal strands*; anterior displacement*; condensed vitreous with strands

\*Expressed in the number of clock hours involved.

**TABLE 2**  
GRADE C PROLIFERATIVE VITREORETINOPATHY DESCRIBED BY CONTRACTION TYPE

TYPE	LOCATION (IN RELATION TO EQUATOR)	FEATURES
1. Focal	Posterior	Starfold posterior to vitreous base
2. Diffuse	Posterior	Confluent starfolds posterior to vitreous base. Optic disk may not be visible
3. Subretinal	Posterior/ anterior	Proliferations under the retina: Annular strand near disk; linear strands; moth-eaten-appearing sheets
4. Circumferential	Anterior	Contraction along posterior edge of vitreous base with central displacement of the retina; peripheral retina stretched; posterior retina in radial folds
5. Anterior displacement	Anterior	Vitreous base pulled anteriorly by proliferative tissue; peripheral retinal trough; ciliary processes may be stretched, may be covered by membrane; iris may be retracted

vitrectomy and produce similar central displacement of the retina (Figs. 6 and 7).

*Type 5*—Anterior displacement of the vitreous base usually occurs in eyes that have previously undergone vitreous surgery especially after use of an intraocular gas or oil tamponade or after trauma. It may also occur, however, in some cases of long-standing untreated proliferative vitreoretinopathy. Proliferative tissue of varying density infiltrates the vitreous base or is present on the surface of remnants of the vitreous base. This tissue extends anteriorly and attaches to the pars plicata of the ciliary body, posterior surface of the iris, or even the pupillary margin.<sup>5</sup> Traction is exerted in two directions: posteroanterior and circumferential. Because the anterior vitreous base is anchored to the pars plana, the posterior vitreous base, the peripheral retina, and even some pars plana epithelium are pulled both forward and inward, creating a circumferential fold of the retina. A trough of varying width and depth appears anterior to this circumferential fold (Fig. 8). In some eyes, the trough may appear to be closed if the peripheral retina is dragged





**Fig. 4** (Machemer and associates). Proliferative vitreoretinopathy Grade C. Type 2, diffuse contraction with multiple confluent retinal folds.

anteriorly and becomes adherent to the anterior structures, with resulting posterior retraction of the iris.

### Method of Grading

Grading takes place by means of a standardized method depicting each type of contraction on a retinal diagram (Fig. 9). The posterior

types of contraction and their location are recorded in the postequatorial portion of the diagram:

Type 1, focal contraction (starfold), is depicted by a large X centered on the starfold.

Type 2, diffuse contraction, is shown by a group of large Xs.

Subretinal proliferation can occur in both the postequatorial and preequatorial parts of the diagram:

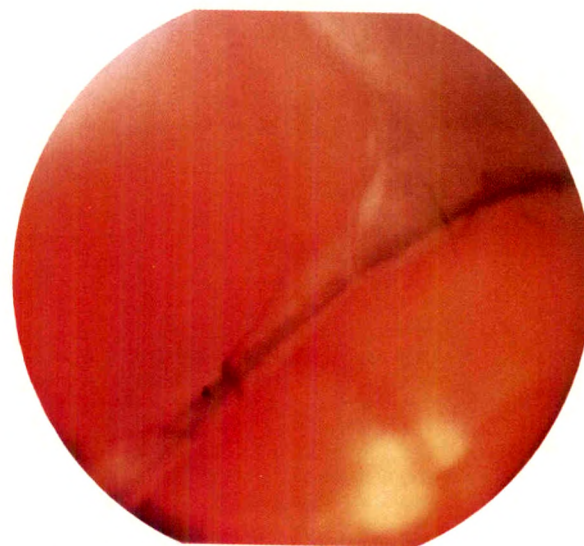
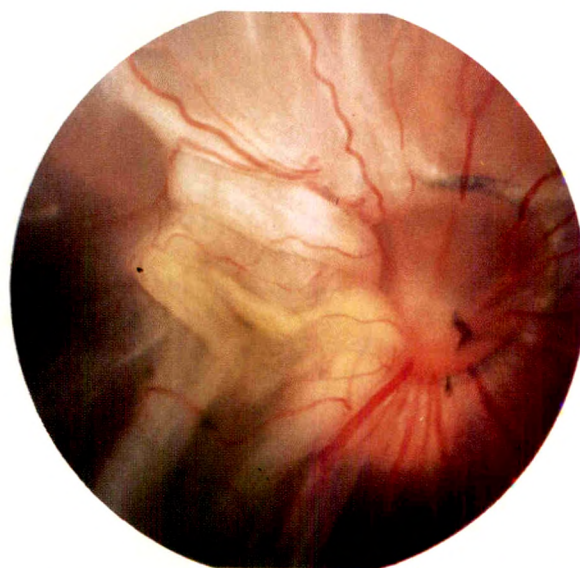
Type 3, subretinal proliferation, is indicated by a broken black line.

The anterior forms of contraction and their location are recorded in the preequatorial portion of the diagram:

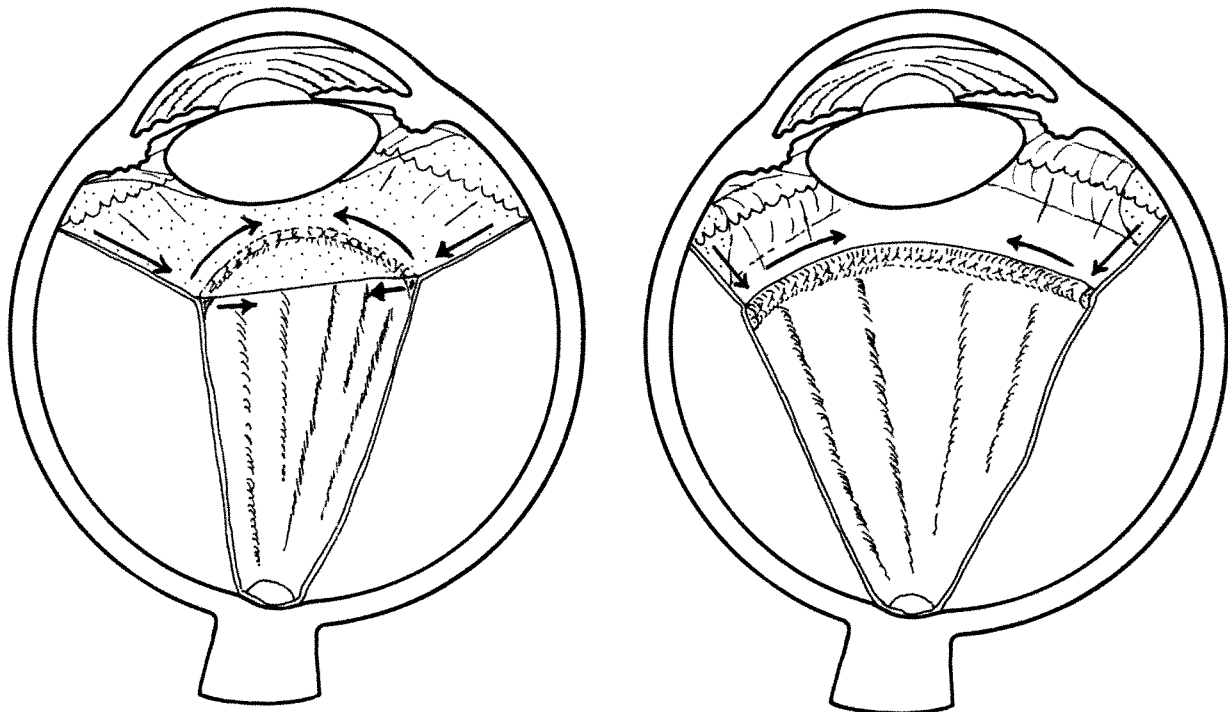
Type 4, circumferential contraction, is shown by a series of small xs.

Type 5, anterior displacement, is depicted like circumferential contraction with arrows pointing anteriorly.

Using a retinal diagram, one can quickly determine the grade and type of proliferative vitreoretinopathy. The grading is illustrated in Figure 9. The total numbers of clock hours of traction in the posterior (postequatorial) and the anterior (preequatorial) portion of the diagram are noted separately. The overall extent of proliferative vitreoretinopathy denotes the number of clock hours of involvement by traction affecting the posterior (CP) and anterior (CA) parts of the retina (for example, CP-6, CA-9).



**Fig. 5** (Machemer and associates). Proliferative vitreoretinopathy Grade C. Type 3. Left, Subretinal contraction causing a semi-annular fold of the retina on nasal side of optic nerve head while ill-defined moth-eaten sheets fold its temporal aspect. Right, A high retinal fold is created by partially pigmented subretinal band with retina draped over it.



**Fig. 6** (Machemer and associates). Proliferative vitreoretinopathy Grade C. Type 4, circumferential contraction with proliferation immediately behind insertion of the posterior hyaloid pulling retina centrally, stretching the retina anterior to it and creating radial folds posteriorly. Schematic drawing of situation in nonvitrectomized eye (left) and vitrectomized eye (right). Arrows show direction of pull.

A more detailed description of the proliferative vitreoretinopathy can be provided by adding the type of contraction to the grade. For example, the classification CP-6, type 1, 2, 3 describes visible postequatorial proliferations (focal, diffuse, subretinal) covering a total of six clock hours. The classification CA-9, type 4, 5 describes preequatorial circumferential proliferations and anterior displacement covering nine clock hours. Because the fovea is the center of the diagram, expressing the extent of the fold in this area in clock hours is difficult. A focal contraction in the macula is judged to represent one clock hour. A diffuse macular contraction covering a larger area is evaluated as if it were slightly shifted to the temporal side.

An optional, even more detailed description can be achieved by adding to each type the number of clock hours involved, similar to those in the grades. Also, proliferations of various types can overlap. Expansion of the example CP-6, type 1, 2, 3 would be represented as CP-6 type 1-1, 2-2, 3-4. In this case the different types all occur within the total extent of the six clock hours. Grade C anterior vitreoretinopathy-9, type 4, 5 would appear as CA-9, type 4-8, 5-3.

## Discussion

The proposed classification summarized in Tables 1 and 2 has been developed to retain as much as possible of the old classification<sup>2</sup> and by drawing on the experience of the Silicone Study group and others.<sup>3,4</sup> The major changes in the grading system from the original 1983 Retina Society classification are the distinction between posterior and anterior abnormalities, addition of a description of contraction types, abandoning the description of the configuration of the retinal funnel, while using clock hours instead of quadrants to describe the extent of the abnormality.

Although the ophthalmoscopic picture of proliferation effects in the postequatorial portions of the eye was reasonably well described under the old system, preequatorial findings were neglected, especially in eyes that had previously undergone vitrectomy. For this reason Grade C has now been subdivided into posterior and anterior regions in order to allow for a description of the clinical picture and types of contraction in anterior proliferative



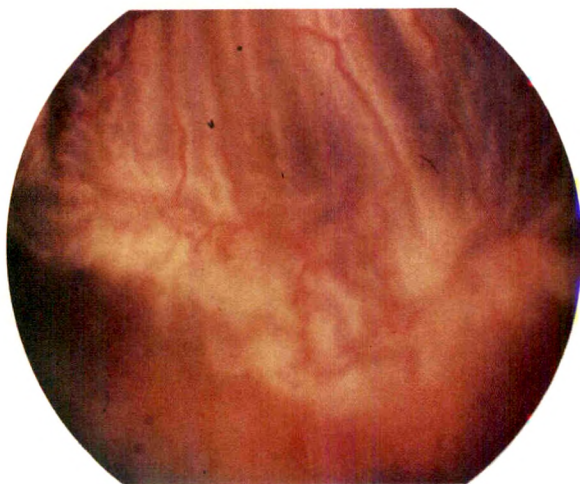


Fig. 7 (Machemer and associates). Proliferative vitreoretinopathy Grade C. Type 4, circumferential contraction.

vitreoretinopathy<sup>6,7</sup> (Table 1). More detailed descriptions of the posterior proliferation effect are made possible by adding the contraction types (focal, diffuse, and subretinal contractions). Anterior proliferation effects are more fully described by addition of references to circumferential contraction<sup>1,3</sup> and anterior dis-

placement (Table 2). Because experience has shown little correlation between funnel size and severity or prognosis, Grade D of the previous classification was abandoned.

Under the old system, although subretinal proliferations were known as part of the clinical picture,<sup>1</sup> no consideration was given to their presence.<sup>2</sup> They have now been included as contraction type 3. Under the revised system, however, still no attempt is made to detail information on these strands, as they are often difficult to define.

The Committee chose not to record information regarding the number, size, and location of retinal breaks in this new classification. Their conclusion was that doing so would only complicate the classification. Furthermore, many retinal holes are hidden or purposefully or inadvertently created during surgery, thereby rendering this information of little value. Individual researchers may, of course, opt to include such information in their own case reports.

No effort was made to define the level of activity of the proliferative process because present knowledge is insufficient to provide objective measures.

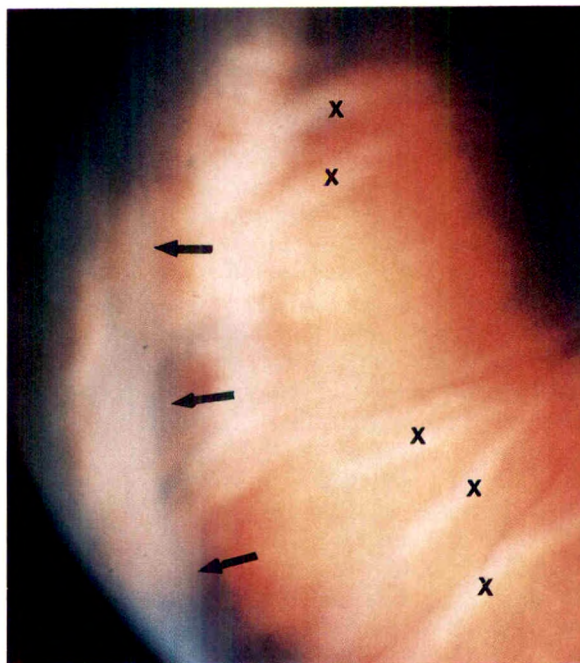
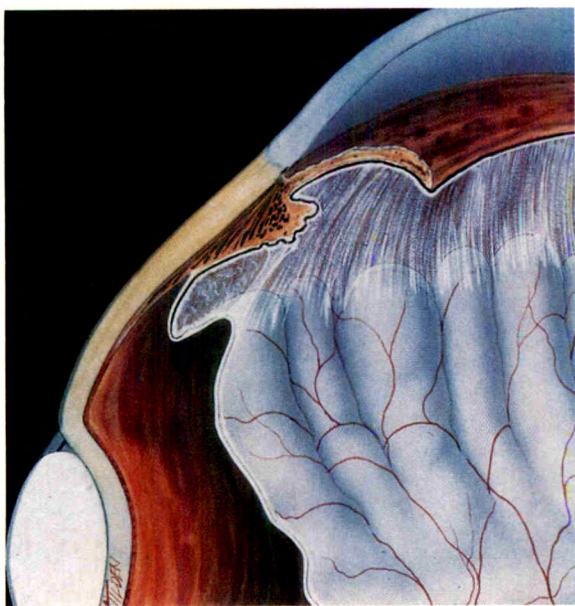


Fig. 8 (Machemer and associates). Proliferative vitreoretinopathy Grade C. Type 5, anterior displacement of the vitreous base. Left, Schematic drawing shows how peripheral retina is pulled forward by fibrous adhesions between vitreous base, ciliary body, and iris to form a retinal trough in a previously vitrectomized and buckled eye. (Courtesy of Springer Verlag, 1988; Freeman and Tolentino, *Proliferative Vitreoretinopathy*, p. 25, Fig. 5.) Right, The most extreme fundus periphery with fibrous tissue in the pars plana area (arrow) causing radial folds (x) in detached retina overlying a circumferential buckle.

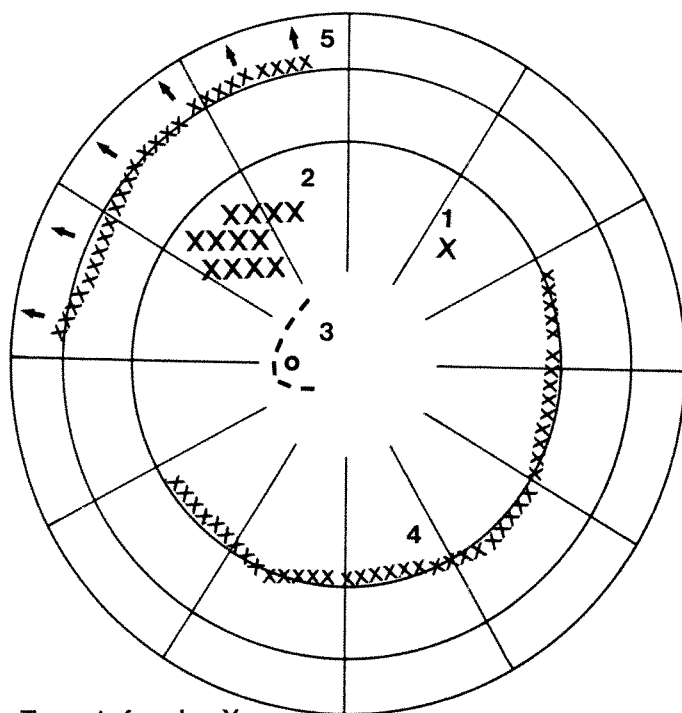


Fig. 9 (Machemer and associates). Retinal diagram to depict the various types of full-thickness retinal folding.

Type 1: focal = X

Type 2: diffuse = X X X

Type 3: subretinal = - -

Type 4: circumferential = xxx

Type 5: anterior displacement =  $\uparrow$ xxx $\uparrow$

In an effort to promote generalized use of this new classification, the Committee has tried to keep it as simple as possible. The committee approach in formulating a classification is advantageous in that a common denominator must be found for differing individual opinions. A classification is best built on ophthalmoscopic and biomicroscopic observations rather than on interpretation of the visible findings. The Committee presents this new classification in the full awareness that it only represents present knowledge and may well need future revisions.

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## Disk Drusen and Angioid Streaks in Pseudoxanthoma Elasticum

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Visual field loss secondary to optic disk drusen became evident before the development of angioid streaks in a patient with pseudoxanthoma elasticum. The incidence of optic disk drusen in cases of pseudoxanthoma elasticum is 20 to 50 times greater than that in the healthy population. We postulate that the abnormal aggregation of macromolecules with a high affinity for calcium (resulting in abnormalities in elastin in cases of pseudoxanthoma elasticum) also develops at the cribriform plate, disrupting axonal flow and leading to disk drusen formation. Pseudoxanthoma elasticum is associated with marked cardiovascular and gastrointestinal morbidity. Moreover, macular hemorrhage and precipitation of angioid streaks have frequently been noted after trauma. Prompt diagnosis of pseudoxanthoma elasticum will allow necessary prophylaxis and must be considered in patients with optic disk drusen.

**P**SEUDOXANTHOMA ELASTICUM is an uncommon inherited disorder with a reported prevalence of one in 160,000 human beings.<sup>1</sup> It affects the elastin in the dermis, arterial walls, and Bruch's membrane, resulting in abnormal mineralization and deposition of phosphorus in the fibrils. Hemorrhage (usually gastrointestinal) is the primary life-threatening complication and affects up to 15% of patients with pseudoxanthoma elasticum, frequently before the onset of cutaneous or ocular symptoms.<sup>2</sup> Eighty-

five percent of the patients develop angioid streaks, usually in the second decade of life,<sup>2</sup> and over 70% develop loss of central vision.<sup>3,4</sup> Optic disk drusen are inherited in an irregular autosomal dominant fashion with a clinical incidence of 3.4/1,000 human beings.<sup>5</sup> Visual field loss is common. Both angioid streaks and optic disk drusen may be associated with subretinal and intraretinal hemorrhages. In this study, we evaluated the association between optic disk drusen and angioid streaks in a family of eight siblings with a history of pseudoxanthoma elasticum.

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### Patients

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A 23-year-old myopic male (Patient II-1) had reduced visual acuity and tunnel vision. On examination, corrected visual acuity was R.E.: 20/16 and L.E.: 20/16. He had bilateral optic disk drusen. Perimetry demonstrated right-field constriction and a left inferonasal scotoma. He was also found to have convergence insufficiency which responded to orthoptic exercises. His old photographs were not available. Seventeen years later he was reviewed routinely at the Royal Victoria Eye and Ear Hospital. Corrected visual acuity was R.E.: 20/60 and L.E.: 20/16. He had developed bilateral peripapillary angioid streaks with peau d'orange mottling in the midtemporal peripheries. Results of a general physical examination disclosed the typical chicken-skin appearance of pseudoxanthoma elasticum on his neck. The diagnosis was confirmed by skin biopsy (Fig. 1). In view of these findings, the extended family was examined.

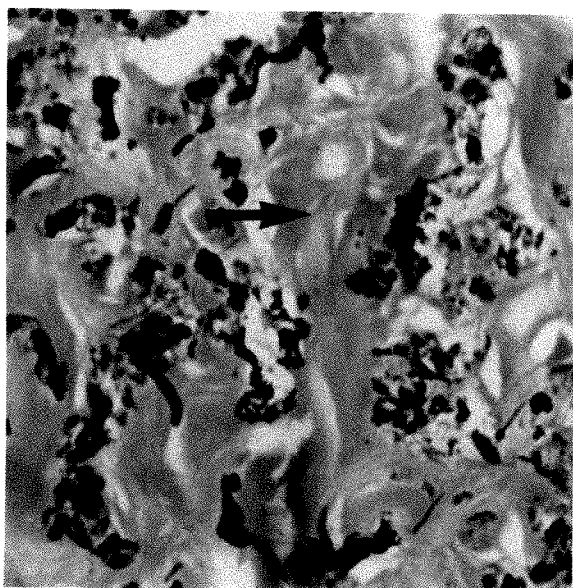
A family tree was constructed (Fig. 2). Patient II-2 had bilateral angioid streaks associated with optic disk drusen and visual field loss. Patient II-4 had angioid streaks associated with peau d'orange mottling and short vertical retinal lines concentric to the disk margin, the

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**Fig. 1** (Coleman and associates). Photomicrograph of histologic section of skin of patient II-1 showing the swollen clumped elastic fibers (arrow) of pseudoxanthoma elasticum (Verhoeff stain,  $\times 250$ ).

cracked-eggshell retinal changes described by Shields and associates.<sup>4</sup> Patients II-3 and II-7 had bilateral angioid streaks; Patient II-7 also had peau d'orange mottling and early retinal pigment epithelial changes at the macula. Patient II-5 had early macular degeneration.

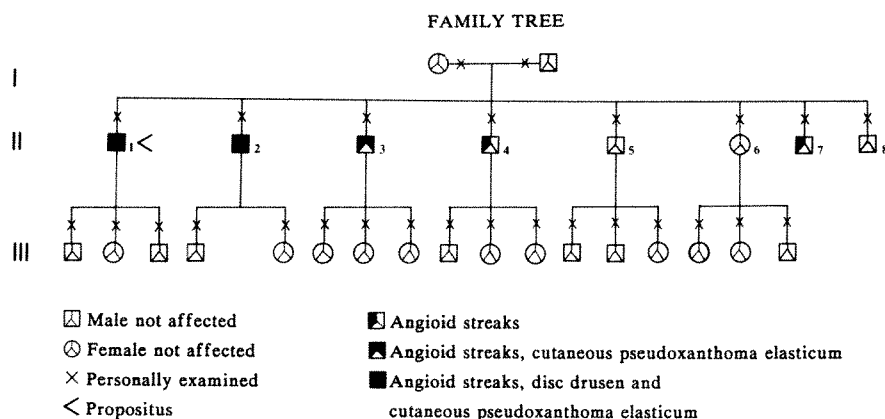
All siblings were examined clinically for pseudoxanthoma elasticum and it was decided that skin biopsies were not needed in view of the obvious ocular manifestations and confirmed diagnosis (Table).

At initial examination, the proband (Patient II-1) had visual field loss associated with optic disk drusen at the age of 23 years. This preceded the development of angioid streaks,

which were detected by routine ophthalmoscopy when the patient was 40 years old. It was only after this discovery that the patient was examined for pseudoxanthoma elasticum, and cutaneous clinical signs were confirmed by skin biopsy.

## Discussion

Pseudoxanthoma elasticum may be inherited as an autosomal dominant (type I and type II) or an autosomal recessive (type I and type II) disorder.<sup>6</sup> Autosomal dominant (type I) is characterized by flexural skin lesions, severe cardiovascular disease, chorioretinal changes, and myopia. Type II autosomal dominant pseudoxanthoma elasticum is a milder variant characterized by focal skin lesions, hyperextensible skin, arched palate, angioid streaks, prominent choroidal vessels, and myopia with minimal vascular manifestations. Type I autosomal recessive pseudoxanthoma elasticum is of intermediate severity between type I and type II autosomal dominant pseudoxanthoma elasticum and shows flexural skin lesions, mild cardiovascular disease, and mild localized chorioretinal changes. Type II autosomal recessive pseudoxanthoma elasticum is the most uncommon variant and is characterized by generalized cutaneous laxity. Skin biopsies may confirm pseudoxanthoma elasticum when there are no clinical signs.<sup>7</sup> Variable expressivity is common in dominantly inherited diseases. The clinical findings in the family suggest a type II autosomal dominant inheritance with incomplete penetrance. However, the lack of clinical signs in the parents would also support an autosomal recessive condition.



**Fig. 2** (Coleman and associates). Family tree showing ocular manifestations of pseudoxanthoma elasticum in eight siblings.



**TABLE**  
SUMMARY OF CLINICAL FINDINGS IN A FAMILY WITH PSEUDOXANTHOMA ELASTICUM

PEDIGREE NO., AGE (YRS) GENDER	SYMPTOMS	OCULAR SIGNS	GENERAL CLINICAL SIGNS
II-1, 40, M	Reduced visual acuity, tunnel vision	Myopia; corrected visual acuity; R.E., 20/16, L.E., 20/16; convergence insufficiency; right constricted field; left inferonasal scotoma at age 23; corrected visual acuity; R.E., 20/60, L.E., 20/16; bilateral optic disk drusen; bilateral angioid streaks; peau d'orange mottling; no change in visual fields at age 40	Pseudoxanthoma elasticum (neck) confirmed by skin biopsy, gastric ulcer
II-2, 38, M	Glare, tunnel vision	Myopia; corrected visual acuity; R.E., 20/20, L.E., 20/20; bilateral optic disk drusen; bilateral angioid streaks; constricted visual fields at age 29; No change at age 38	Pseudoxanthoma elasticum (neck), peptic ulcer
II-3, 36, M	None	Myopia; corrected visual acuity; R.E., 20/20, L.E., 20/20; bilateral angioid streaks	Pseudoxanthoma elasticum (neck), gastric ulcer
II-4, 35, M	None	Myopia; corrected visual acuity; R.E., 20/20, L.E., 20/20; bilateral angioid streaks; bilateral peau d'orange mottling; cracked egg-shell appearance	None
II-5, 32, M	None	Emmetropia; visual acuity; R.E., 20/20, L.E., 20/20; macular degeneration; peripapillary atrophy	None
II-6, 30, F	None	Severe myopia; corrected visual acuity; R.E., 20/20, L.E., 20/20; myopic degeneration; prominent choroidal vasculature	None
II-7, 25, M	None	Emmetropia; visual acuity; R.E., 20/20, L.E., 20/20; bilateral angioid streaks; peau d'orange mottling; macular pigment changes	None
II-8, 23, M	None	Emmetropia; visual acuity; R.E., 20/16, L.E., 20/16	None
I-1, 68, M	None	Presbyopia; corrected visual acuity; R.E., 20/20, L.E., 20/20	None
I-2, 65, F	None	Severe myopia; corrected visual acuity; R.E., 20/20, L.E., 20/20; prominent choroidal vessels; increased myopia	None

Eighty-five percent of patients with pseudoxanthoma elasticum demonstrate angioid streaks.<sup>2</sup> These angioid streaks usually develop after the second decade and may develop up to the fifth decade of life. Loss of visual acuity is common and over 60% have a visual acuity less than 20/200 after the age of 50 years. This results from foveal involvement by a streak or is because of the development of a subretinal neovascular membrane.<sup>3,4</sup> Macular degeneration usually develops at a young age<sup>8</sup> and may precede the appearance of a streak.<sup>4</sup> Other ocular findings include peau d'orange mottling, cracked-eggshell appearance, salmon spots, and optic disk drusen. Disk drusen have been associated with these clinical signs before the development of angioid streaks<sup>9</sup> and have been well described in siblings of these patients.<sup>10,11</sup> They may, however, as demonstrated by the propositus, be the only ocular manifestation of pseudoxanthoma elasticum.

Optic disk drusen are inherited as an irregular autosomal dominant trait. Lorentzen<sup>5</sup> reported an incidence of 0.34% in a study of 3,200 eyes. In pseudoxanthoma elasticum, the incidence is between 6% (five of 86 eyes)<sup>12</sup> and 16% (ten of 112 eyes).<sup>4</sup> Visual field loss as a result of disk drusen develops in over 70% of patients with optic disk drusen and is usually in the form of nerve-fiber bundle defects or concentric constriction. Central vision is almost always spared,<sup>13-15</sup> although vision may deteriorate suddenly because of direct compression of a vessel by the drusen.<sup>16-18</sup>

There is a high risk of visual field loss in patients with both angioid streaks (central loss) and optic disk drusen (peripheral loss). Patients with both conditions may be at an even greater risk of debilitating visual impairment. A review of the literature discloses that the combination of angioid streaks and optic disk drusen has been described exclusively in patients with

pseudoxanthoma elasticum. We have recently seen both of these clinical signs in a patient with Waldenström's macroglobulinemia and believe that they may sometimes coexist in other diseases. Erkkila<sup>18</sup> hypothesized that the increased incidence of clinical disk drusen in patients with pseudoxanthoma elasticum may be because of enhanced expressivity of the disk drusen gene. Recent work, however, on the pathogenesis of pseudoxanthoma elasticum lends support to a probable common, genetically determined biochemical cause.

Pseudoxanthoma elasticum was originally considered to be a result of a primary abnormality of elastin.<sup>19</sup> Yamamura and Sano<sup>20</sup> demonstrated mineralized elastic fibers in a granulosomatous matrix composed of fibrinogen, collagenous protein, and glycoprotein. More recently, Walker, Frederickson, and Mayes<sup>21</sup> used immunocytochemistry and x-ray analysis to show that the earliest abnormality is the accumulation of polyanions in the pseudoxanthoma elasticum dermis. These polyanions have a high affinity for calcium and serve as the initiating factor in mineralization. They noted inconsistent collagen mineralization in addition to the elastin mineralization and hypothesize that the basic genetic abnormality is not one of elastin or calcium metabolism, but of glycoproteins or glycosaminoglycans. These abnormal macromolecules aggregate and then infiltrate and adhere to elastic fibers, resulting in mineralization and abnormal defects in collagen assembly.

We believe that these macromolecules may also have a high affinity for the elastic fibers of the cribriform plate. Optic disk drusen are located in front of the lamina cribrosa.<sup>22,23</sup> Interference with axoplasmic transport at this point produces accumulations of axoplasmic material.<sup>24</sup> Ultrastructural studies by Tso<sup>25</sup> have indicated that alteration in axonal transport, with abnormal axonal metabolism, leads to intracellular mitochondrial mineralization. Axonal rupture allows extrusion of these mitochondria into the extracellular space and mineralization of these microbodies continues to form drusen. We suggest that in patients with pseudoxanthoma elasticum, an abnormal accumulation of polyanions at the elastin of the cribriform plate results in disruption of axonal transport and subsequent formation of drusen. Disruption of axonal transport would account for the high clinical incidence of disk drusen in these patients. The actual incidence is probably much higher because over 80% of drusen are

buried in the disk.<sup>23</sup> We would support this hypothesis with histochemical and ultrastructural evidence comparing the connective tissue of the lamina cribrosa in the eyes of patients with pseudoxanthoma elasticum with age-matched healthy eyes, but must await available material.

From a practical point of view, as demonstrated by the propositus, optic disk drusen may be the earliest clinical manifestation in patients with pseudoxanthoma elasticum, with possible concomitant cardiovascular and gastrointestinal morbidity. It is well documented that ocular trauma in patients with pseudoxanthoma elasticum predisposes to the development of angioid streaks and subsequent visual loss.<sup>7,10,25,26</sup> It is, therefore, our view that all patients with optic disk drusen should have a dermatologic assessment for evidence of pseudoxanthoma elasticum, so that prudent advice with regard to systemic symptoms and ocular trauma may be given.

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#### OPHTHALMIC MINIATURE

Him and his two colors of eyes. I don't know what that particular ocular condition is called, maybe Crayola in the genes, but on Riley the unmatched hues were damn disconcerting—his way of looking at you in two tones, flat gray from one side and bright blue the other. Rampant right up to his irises.

Ivan Doig, *Ride With Me, Mariah Montana*  
New York, Atheneum, 1990, p. 19

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# Regional and Long-term Variability of Fundus Measurements Made With Computer-Image Analysis

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Eydie Miller, M.D., and Joseph Caprioli, M.D.

We studied the variability of optic disk and peripapillary nerve fiber layer surface contour measurements made by use of computer-image analysis. Six hundred twenty-five measurements of surface contour were made on each eye by use of simultaneous stereoscopic videography. Regional differences in short-term measurement variability were studied in 12 eyes (six normal and six glaucomatous), each imaged nine times over several days. The widths of the 95% confidence interval for the measurements averaged 82  $\mu\text{m}$  for the juxta-papillary surface and 132  $\mu\text{m}$  for the disk surface. Measurements of peripapillary surface contour were significantly less variable than were measurements of the disk surface ( $P = .000$ ). The greatest variability was detected along large blood vessels and at steep contours. Long-term variability was studied in a separate group of 30 clinically stable patients with glaucoma, each imaged three to six times over a period of more than one year. The widths of the 95% confidence intervals were 132  $\mu\text{m}$  for the peripapillary surface and 217  $\mu\text{m}$  for the disk surface. The long-term variability was significantly greater than the short-term variability ( $P = .000$ ). The peripapillary nerve fiber layer surface, located away from the margins of large vessels, may provide the most dependable measurements of contour. These estimates of long-term variability of optic disk and peripapillary contour

measurements provide clinically relevant confidence intervals with which to detect progressive glaucomatous nerve fiber damage.

THE GOALS OF computer-image analysis of the optic nerve in glaucoma are to distinguish glaucomatous from nonglaucomatous eyes at an early stage of the disease; and to enhance the detection of progressive optic nerve damage. Standard computer-disk measurements (cup/disk ratio, disk rim area, and cup volume) are reproducible, but do not discriminate well between clinically normal eyes and eyes with early glaucomatous damage.<sup>1-5</sup> Measurements of peripapillary nerve fiber layer surface contour have recently been introduced to take greater advantage of the quantitative depth information that computed-image analysis can provide.<sup>6</sup> This study was undertaken to identify important regional differences in measurement variability of disk and peripapillary nerve fiber layer surface contour and to develop confidence intervals to detect clinically significant change of the optic nerve and nerve fiber layer structure in glaucoma.

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## Patients and Methods

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Computed-image analysis of digitized videographic images of the optic disk and peripapillary retina of clinically normal subjects and patients with glaucoma was used for this study. Digitized fundus images and preliminary topographic analyses of the disk and peripapillary surfaces were obtained with the Rodenstock Analyzer (Rodenstock Instruments, Munich, Germany). Descriptions of this instrument and the reproducibility of optic nerve head measurements have been previously reported.<sup>2-5</sup> Depth images from the Rodenstock Analyzer were transmitted to an external computer (IBM PC/AT) on which a 25  $\times$  25 array of depth

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measurements was constructed that spanned a circular area (approximate diameter, 2.5 mm) centered at the optic disk. Each number in the array was an average depth, in microns, of a 100- $\mu$ m square area. The Littmann method was used with corneal curvature and ultrasonic axial length measurements to correct all measurements for the magnification of each eye.<sup>7</sup> Relative depths (or heights) were measured with respect to a standardized retinal reference plane.<sup>8</sup> Three areas of the retinal surface (located temporally, supranasally, and inferonasally) were used to construct the reference plane, which had a defined height of zero. Measurements of the disk and peripapillary surfaces were made relative to this reference plane; positive values were distances below the plane, negative values were distances above it.

Clinically normal subjects were staff or persons accompanying patients to the Yale Eye Center. None had a history of eye disease. All subjects were over 40 years of age, had a spherical equivalent refraction of -5 to +5 diopters, normal results of eye examination, a clinically normal visual field tested by automated threshold perimetry (Octopus programs 32 or G1, Interzeag, Schlieren, Switzerland; Humphrey programs 24-2 or 30-2, Humphrey Instruments, San Leandro, CA), and no family history of glaucoma. Slit-lamp biomicroscopy, tonometry, gonioscopy, dilated indirect ophthalmoscopy, stereoscopic optic disk photography, and videographic photography were performed.

Patients with glaucoma were over 40 years of age, had a spherical equivalent refraction of -5 to +5 diopters, and had an eye examination as described. Each had a history of increased intraocular pressure before initiation of treatment of glaucoma and had typical glaucomatous visual field defects as determined by automated perimetry. Typical visual field loss was defined as one of the following: three contiguous points of 5 dB or more loss in the superior or inferior arcuate regions as compared with perimeter-defined age-matched controls; two contiguous points with at least a 10-dB loss in the same areas; or a 10-dB difference across the nasal horizontal midline at two or more adjacent points.

Regional differences in variation were evaluated in 12 eyes of 12 patients (six healthy and six glaucomatous eyes randomly chosen); each had nine sets of measurements made over a period of several days. Long-term variation was studied in 30 consecutive, clinically stable patients with glaucoma who had been monitored

for longer than one year; had an intraocular pressure less than or equal to 22 mm Hg throughout the period; had visual acuity measurements within two Snellen lines of baseline value; had a stable treatment regimen defined as either no change in medication over the period of the study or a change in medication because of side effects, but intraocular pressure remained less than or equal to 22 mm Hg; had stable visual fields tested by use of automated threshold perimetry (Octopus programs G1 or 32, or Humphrey programs 24-2 or 30-2); and had an unchanged disk appearance that was determined by examination of sequential stereoscopic photographs. Each patient had videophotography performed for image analysis at each of three to six office visits over this time period that coincided with the times of their visual field tests and disk photography. One set of measurements of disk and peripapillary surface contour was made at each of these visits.

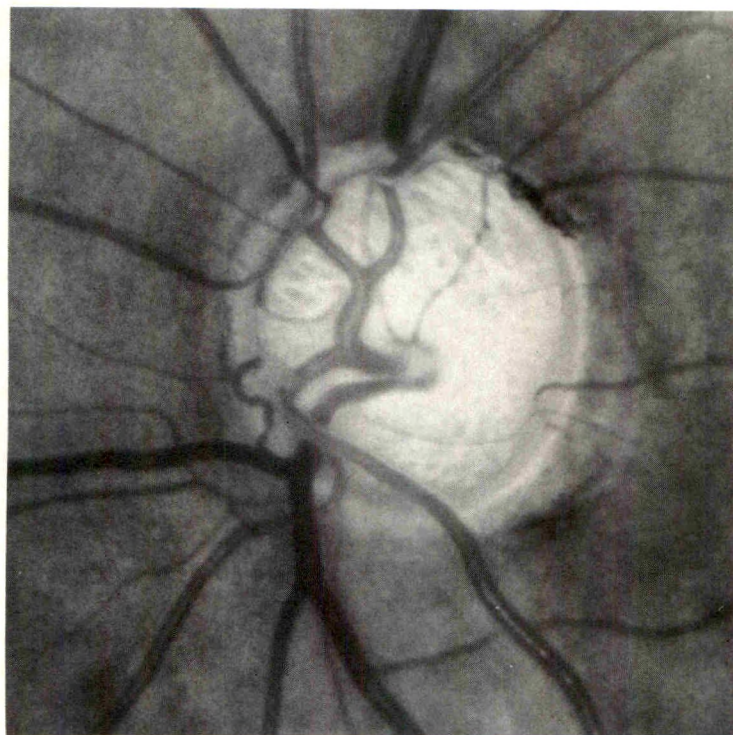
To study regional differences in variability, variability maps were constructed for each patient (Figs. 1 and 2). Variability was defined as the width of the 95% confidence interval for repeated measurements, in micrometers, at each of the 625 locations. The width of the 95% confidence interval was determined by 95% confidence interval =  $2 \times SD \times t_{.05}$ , where SD is the standard deviation of repeated measurements and  $t_{.05}$  is the value of Student's *t*-test at the  $P = .05$  level (two-tailed) for the appropriate degrees of freedom ( $n - 1$ ). These were averaged separately over the entire peripapillary surface and the entire disk surface. Student's *t*-test was used to determine the statistical significance of the differences between means.

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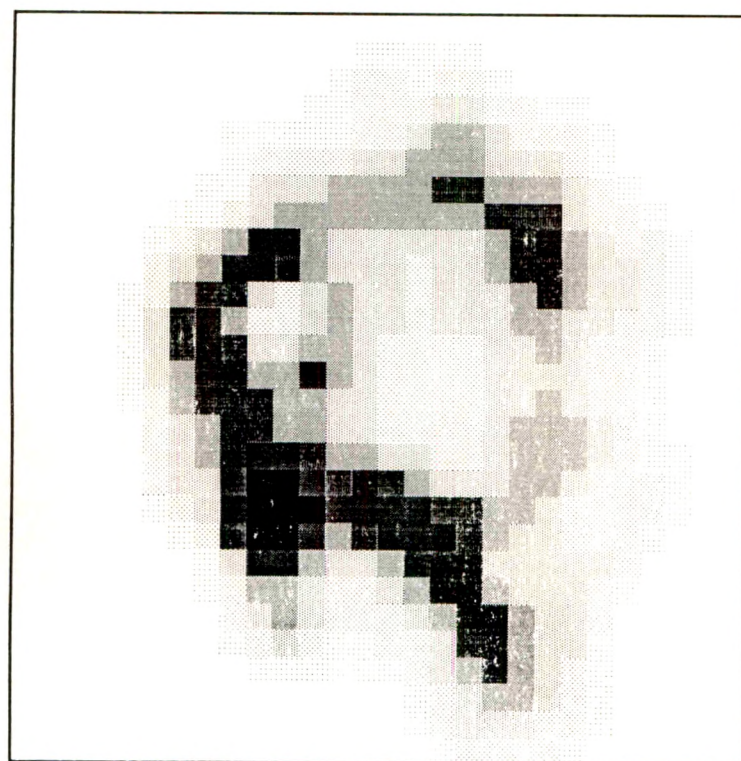
## Results

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The  $25 \times 25$  matrices of fundus depth measurements were used to construct variability maps to facilitate the regional analysis of variability (Figs. 1 and 2). The average 95% confidence interval for repeated measurements of the peripapillary surface in the short-term group was 82  $\mu$ m compared with 132  $\mu$ m for the disk surface. This regional difference was statistically significant ( $P = .000$ ). Measurements along large blood vessels and along steep contours of the cup had the greatest variability, and the 95% confidence interval sometimes exceeded 330  $\mu$ m in such areas. The variability at



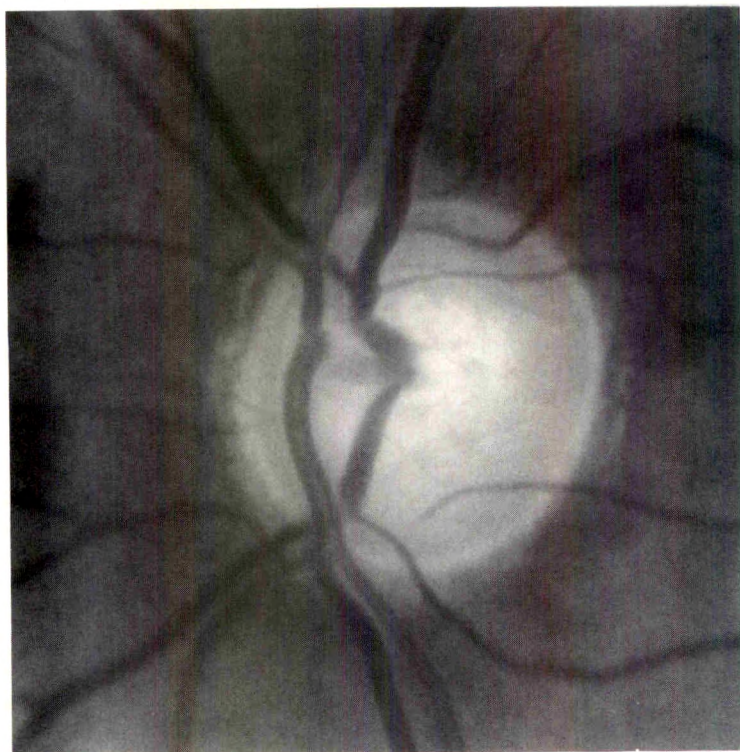
**Fig. 1** (Miller and Caprioli). Regional variation of disk and peripapillary surface contour measurements in a glaucomatous eye. Top, Fundus photograph. Bottom, Corresponding variability map that shows the width of the 95% confidence interval of repeated measurements at each of the 625 locations of the contour matrix. Note the increased variability along large trunks of blood vessels and at steep margins of the cup.



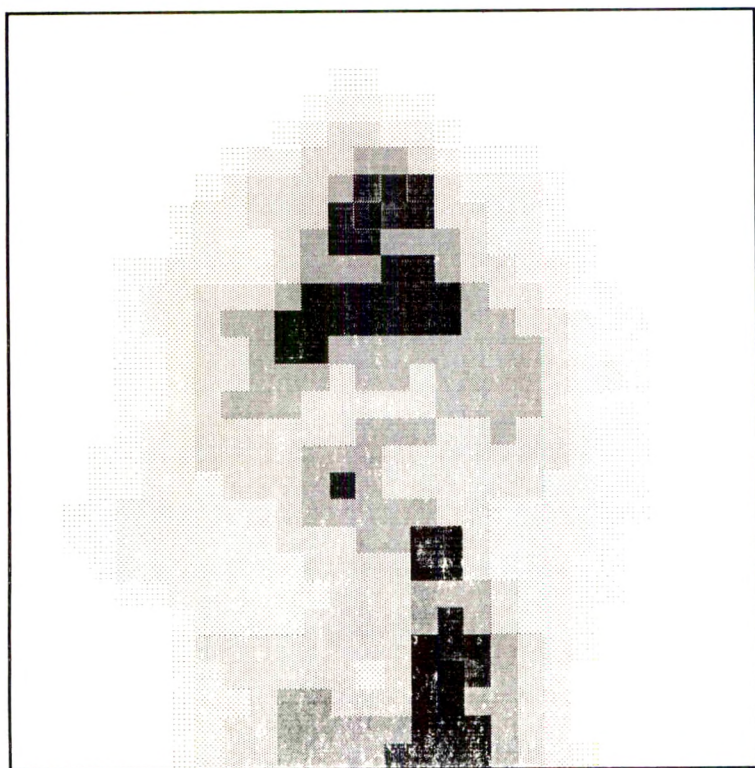
#### Microns

- 250
- 225
- 200
- 175
- 150
- 125
- 100
- 75
- 50
- 25
- 0





**Fig. 2** (Miller and Caprioli). Regional variation of disk and peripapillary surface contour measurements in a glaucomatous eye. Top, Fundus photograph. Bottom, Corresponding variability map that shows the width of the 95% confidence interval of repeated measurements at each of the 625 locations of the contour matrix. Note the increased variability along large trunks of blood vessels and at steep margins of the cup.



**Microns**

- 200
- 180
- 160
- 140
- 120
- 100
- 80
- 60
- 40
- 20
- 0

peripapillary areas away from the margins of large vessels was such that the 95% confidence interval was frequently less than 40  $\mu\text{m}$ . The average confidence interval for the entire surface in the patients with glaucoma (124  $\mu\text{m}$ ) was significantly greater ( $P = .03$ ) than that in the clinically normal subjects (82  $\mu\text{m}$ ).

The long-term variation group of patients with stable glaucoma had an average 95% confidence interval for repeated contour measurements of 171  $\mu\text{m}$  for the entire image surface. The average 95% confidence intervals were 132  $\mu\text{m}$  for the peripapillary surface and 217  $\mu\text{m}$  for the disk surface. This regional difference was statistically significant ( $P = .000$ ). The variability in the long-term group was significantly greater than that in the short-term group ( $P = .02$ ).

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### Discussion

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Clinically detectable structural damage to the optic nerve head and nerve fiber layer often precede glaucomatous abnormalities of the visual field.<sup>9-11</sup> The ability to measure accurately small changes in the surface structure of the disk or nerve fiber layer could enhance the early detection of progressive optic nerve damage. Computer-image analysis has been used to measure certain structural variables of the disk and nerve fiber layer. It can generate reproducible measurements of cup/disk ratio, disk rim area, and cup volume.<sup>2,3,5</sup> Variability of surface contour measurements of the disk and peripapillary retina have also been reported.<sup>6,12</sup>

Dandona, Quigley, and Jampel<sup>12</sup> studied the variability of contour measurements at 400 to 650 locations in the optic nerve head and peripapillary retina with the Humphrey Retinal Analyzer. Ten repeated measurements were made in a single session. Variability was greater in subjects with increased intraocular pressures than it was in clinically normal control subjects, and the width of 95% confidence intervals for repeated measurements ranged between 166  $\mu\text{m}$  and 261  $\mu\text{m}$ . Variability was greater for contour measurements of the peripapillary retina than for measurements of the optic disk.

We studied the regional differences in optic disk and peripapillary contour measurements in clinically normal subjects and patients with glaucoma and the long-term variation of depth measurements in clinically stable patients with

glaucoma. Variability maps showed that variability was greatest along large blood vessels and along steep walls of the cup. The 95% confidence interval for repeated measurements in some cases exceeded 330  $\mu\text{m}$  in these localized areas. The least variability was detected in the peripapillary retina, away from the margins of the large blood vessels. The 95% confidence interval for measurements in these locations was frequently less than 40  $\mu\text{m}$ . Data from the long-term variation group confirmed these patterns of regional variability. There was greater overall variability of the long-term measurements in patients with glaucoma (132  $\mu\text{m}$  for the peripapillary surface and 217  $\mu\text{m}$  for the disk surface) than for short-term measurements. These larger confidence intervals for long-term measurements are required when evidence for clinically significant change over an appropriate time interval is sought.

We found that measurements of the peripapillary surface were less variable than measurements of the disk surface. Dreher, Tso, and Weinreb<sup>13</sup> used laser tomographic scanning to make depth measurements of the optic nerve head and peripapillary retina, and also noted less variation in the peripapillary area than in the nerve head. Depth measurements in this study were made with respect to a standardized retinal reference plane. This technique markedly reduces the overall variability of repeated measurements.<sup>14</sup> The projection of illuminated stripes on the fundus provides areas of image contrast that assist the automatic algorithms to make depth measurements, particularly in areas that do not have an abundance of inherent image contrast or detail such as peripapillary areas located away from large blood vessels. These differences in technique may help explain the differences between the results of this study and those of Dandona, Quigley, and Jampel.<sup>12</sup>

The optic nerve head may be less of a static structure than previously thought; the conformation of the optic nerve head in an individual eye seems to depend on intraocular pressure. Dramatic changes in its structure occur with large reductions in intraocular pressure.<sup>15-18</sup> Reversible changes in optic nerve head conformation have been demonstrated with increased intraocular pressure.<sup>16</sup> It would be reasonable to expect that small changes, heretofore clinically undetectable, occur with relatively smaller changes of intraocular pressure, and would contribute to the variability of long-term measurements of the optic nerve head. The magni-



tude of the confidence intervals for change was larger in the long-term group than in the subjects who were imaged over a short period of time. Long-term changes of intraocular pressure as well as other factors such as camera recalibrations, changes in ocular media, and perhaps pupil size may all contribute to this additional component of variability found with long-term follow-up.

Shields<sup>5</sup> indicated that although the reproducibility and accuracy of computed structural measurements are important, the most useful variables for clinical use have yet to be defined. For example, relative nerve fiber layer surface height is more sensitive and specific than standard disk measurements (cup/disk ratio, disk rim area, and cup volume) to separate clinically normal patients from patients with glaucoma.<sup>6</sup> The best areas to measure depth would be those at which measurements were least variable and most likely to change with glaucomatous damage. The juxtapapillary nerve fiber bundles at the superior and inferior poles of the disk seem the most likely candidates at present.

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## Treatment of Pseudotumor Cerebri by Primary and Secondary Optic Nerve Sheath Decompression

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Thomas C. Spoor, M.D., John M. Ramocki, M.D., Matthew P. Madion, M.D.,  
and Michael J. Wilkinson, M.D.

We performed optic nerve sheath decompression in 53 patients (101 eyes) with pseudotumor cerebri and visual loss. Sixty-nine eyes (85 patients) with acute papilledema uniformly had improved visual function after optic nerve sheath decompression. Of 32 eyes with chronic papilledema (18 patients), only ten had improved visual function after optic nerve sheath decompression. This difference was significant ( $P = .0001$ ). Thirteen eyes required secondary or tertiary optic nerve sheath decompression after an initial successful result. Eleven of 13 eyes had improved visual function after repeat optic nerve sheath decompression. We believe that patients with acute papilledema and visual loss should be offered optic nerve sheath decompression, and if symptoms recur, repeat optic nerve sheath decompression is a safe and effective treatment option.

**P**SEUDOTUMOR CEREBRI is characterized by increased intracranial pressure, lack of demonstrable intracranial abnormality, clinically normal cerebrospinal fluid, and papilledema. Visual loss develops in 20% to 50% of patients.<sup>1,2</sup> Management options for this disease are protean and controversial. Treatments include administration of systemic corticosteroids, carbonic anhydrase inhibitors, and weight loss.<sup>3</sup> Surgical treatment includes repeat lumbar punctures, neurosurgical shunting procedures, and optic nerve sheath decompression.<sup>3</sup> The optic nerve sheath decompression

has been shown to be an effective and safe treatment for pseudotumor cerebri and visual loss.<sup>4,5</sup>

We treated 53 patients (101 eyes) with pseudotumor cerebri and visual loss with optic nerve sheath decompression. Eyes operated on early in the course of acute papilledema had a much better recovery of vision than those with chronic atrophic papilledema.

We successfully performed secondary and tertiary optic nerve sheath decompression in 13 eyes with visual dysfunction after an initially successful optic nerve sheath decompression.

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### Patients and Methods

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Optic nerve sheath decompressions were performed on 101 eyes from 53 patients with pseudotumor cerebri by one of us (T.C.S.) over a four-year period. Before surgery, patients underwent a neuro-ophthalmic examination including Goldmann or automated (visual field analyzer, 30-2 program, Allergan Humphrey, San Leandro, California) perimetry, optic disk photography, and standardized echography measuring retrobulbar optic nerve sheath diameters. Patients with papilledema underwent appropriate neuro-imaging followed by lumbar puncture measuring intracranial pressure to confirm the diagnosis of pseudotumor cerebri. Pseudotumor cerebri was diagnosed on the basis of the presence of papilledema, normal results of neuro-imaging studies, increased intracranial pressure by lumbar puncture, and clinically normal cerebrospinal fluid protein and cell contents. Unilateral or bilateral sixth nerve paresis was the only localizing neuro-ophthalmic clinical sign considered compatible with the diagnosis of pseudotumor cerebri.

All optic nerve sheath decompressions were performed via a transconjunctival medial orbi-

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totomy, disinserting the medial rectus muscle and exposing the retrobulbar optic nerve sheath. Using the operating microscope and microsurgical instrumentation, the surgeon incised the optic nerve sheath and fenestrated it in one or more locations.<sup>4,5</sup>

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## Results

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Thirty-five patients (69 eyes) with acute papilledema and visual loss secondary to pseudotumor cerebri underwent optic nerve sheath decompression (Table 1). Ages ranged from six to 72 years (mean, 32.3 years). Postoperative follow-up ranged from two to 48 months (mean, 18.1 months). All eyes undergoing primary optic nerve sheath decompression had initial improvement in visual function and obviation of obscurations. Sixteen patients (29 eyes) underwent automated perimetry (Humphrey visual field analyzer, 30-2 program, Allergan Humphrey, San Leandro, California) before and after optic nerve sheath decompression. Quantitative improvement in visual function was significant ( $P = .0001$ ) after optic nerve sheath decompression. Complications after primary optic nerve sheath decompression included transient diplopia, pupillary dysfunction, hypotonia, and peripapillary hemorrhages (two eyes). These all resolved without adverse sequelae and were not considered significant. Thirteen eyes required secondary (ten eyes) or tertiary (three eyes) optic nerve sheath decompression after initial successful primary surgery (Table 2).

Eighteen patients (32 eyes) with chronic atrophic papilledema and visual loss secondary to pseudotumor cerebri underwent optic nerve sheath decompression (Table 3). Ages ranged from 7 to 57 years (mean, 32.7 years). Postoperative follow-up ranged from three to 46 months (mean, 14.6 months).

Visual improvement after optic nerve sheath decompression in eyes with chronic atrophic papilledema (Table 3) was not nearly as impressive as in eyes with acute papilledema (Table 1). Only ten of 32 eyes demonstrated improved visual function. The difference between the visual improvement in patients with acute and chronic papilledema is significant ( $P = .0001$ ). Only one patient with chronic atrophic papille-

dema required a repeat optic nerve sheath decompression, possibly because of the increased difficulty assessing progressive visual dysfunction in poorly sighted eyes. Many patients in this group were refractory to medical and surgical treatment for their pseudotumor cerebri. Long-term medical treatment regimens often failed to prevent visual dysfunction, as did recurrent ventriculoperitoneal and lumboperitoneal shunting (Table 3).

Eleven patients (13 eyes) underwent repeat optic nerve sheath decompression for visual deterioration after initial successful surgery (Table 2). Three eyes each underwent three optic nerve sheath decompressions. Two of these eyes had successful results; the third failed to regain visual function. Twelve eyes had initial successful responses to primary optic nerve sheath decompression, but subjective recurrence of visual obscurations and/or objective evidence for deterioration of visual function prompted repeat optic nerve sheath decompressions. Visual results were successful, with 11 of 13 eyes showing improved visual acuity or visual field after a repeat optic nerve sheath decompression. Surgical complications included pupillary dysfunction (two eyes, short ciliary nerve injury); peripapillary hemorrhages (one eye, short ciliary vessel injury); chemosis with dellen formation (excessive manipulation); and chorioretinal scarring (excessive retraction of globe). No patients lost visual function as a result of repeat optic nerve sheath decompression.

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## Discussion

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Optic nerve sheath decompression is a safe and effective treatment for patients with papilledema and visual loss secondary to pseudotumor cerebri.<sup>3-5</sup> Our data suggest that patients with acute papilledema who undergo optic nerve sheath decompression have significantly better visual results than do patients with chronic atrophic papilledema ( $P = .0001$ ). This difference in visual prognosis is intuitively obvious in that early surgery relieves the pressure on the optic nerve fibers before permanent damage or attrition of axons.

Most patients with chronic atrophic papilledema who underwent optic nerve sheath de-

**TABLE 1**  
**CHARACTERISTICS OF PATIENTS WITH PSEUDOTUMOR CEREBRI AND ACUTE PAPILLEDEMA UNDERGOING OPTIC NERVE SHEATH DECOMPRESSION**

CASE NO., AGE (YRS), GENDER	VISUAL ACUITY		VISUAL FIELD		FOLLOW-UP (mos)	PRIMARY SYMPTOMS	COMMENT
	EYE	PREOPERATIVE POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE			
1, 32, F R.E.	20/20	20/20	Constriction, 20-30 degrees	Full	20	—	Lithium
1, 32, F L.E.	20/20	20/20	Constriction, 20-30 degrees	Full	19	Obscurations, headache	—
1, 32, F L.E.	20/20	20/20	Constriction, 20-30 degrees	Full	6	—	Reoperated on
2, 20, F R.E.	20/40	20/20	Constriction, 20-30 degrees	Full	2	—	Systemic central nervous system lupus erythematosus, died 3 months after surgery
2, 20, F L.E.	20/800	20/25	Constriction, central scotoma	Improved	2	—	—
3, 28, F L.E.	20/25	20/20	Constriction, 20-30 degrees	Full	4	Obscurations	Obscurations, asymmetric papilledema
3, 28, F L.E.	20/20	20/20	Constriction, 20-30 degrees	Full	5	—	—
3, 28, F L.E.	20/20	20/20	Constriction, 20-30 degrees	Full	27	—	Reoperated on twice
4, 35, F R.E.	20/25	20/20	Constriction, 20-30 degrees	Full	22	Loss of vision, headache	—
4, 35, F L.E.	20/30	20/20	Constriction, 20-30 degrees	Full	23	—	—
5, 32, F R.E.	20/25	20/20	Constriction, 20-30 degrees	Full	2	Headache	Acetazolamide intolerant
6, 30, F R.E.	20/20	20/20	Constriction, 20-30 degrees	Full	8	Obscurations	Intracranial pressure > 600 mm cerebrospinal fluid, poor compliance
7, 31, F R.E.	20/25	20/25	Constriction, 20-30 degrees	Full	2	Obscurations	Asymmetric papilledema
7, 31, F R.E.	20/30	20/25	Constriction, 20-30 degrees	Full	26	Obscurations	Reoperated on
8, 28, F R.E.	20/25	20/25	Constriction, 20-30 degrees	Full	24	—	Furosemide, acetazolamide, prednisone, intractable intracranial pressure
8, 28, F L.E.	20/25	20/25	Constriction, 20-30 degrees	Partially improved	2	Obscurations	>560 mm cerebrospinal fluid
8, 28, F L.E.	20/25	20/20	Constriction, 20-30 degrees	Full	22	—	Reoperated
9, 32, F L.E.	20/25	20/20	Constriction, 20-30 degrees	Full	6	Obscurations	—
9, 32, F R.E.	20/20	20/20	Constriction, 20-30 degrees	Full	28	—	—
9, 32, F L.E.	20/30	20/25	Constriction, 20-30 degrees	Full	20	—	Reoperated on
9, 32, F L.E.	20/50	20/25	Constriction, 20-30 degrees	Full	1	Obscurations	Reoperated on twice
10, 33, F L.E.	20/25	20/20	Constriction, 20-30 degrees	Full	1	Obscurations Headache	Intractable intracranial pressure Lumboperitoneal shunt six times

(Continued on pg. 180)



**TABLE 1 (continued)**  
**CHARACTERISTICS OF PATIENTS WITH PSEUDOTUMOR CEREBRI AND ACUTE PAPILLEDEMA UNDERGOING OPTIC NERVE SHEATH DECOMPRESSION**

CASE NO., AGE (YRS), GENDER	VISUAL ACUITY		VISUAL FIELD		FOLLOW-UP (mos)	PRIMARY SYMPTOMS	COMMENT
	EYE	PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE		
11, 22, F L.E.	20/70	20/25	Constriction, 10-20 degrees	Full	7	Obscurations	Posttraumatic increased intracranial pressure
12, 31, F L.E.	20/50	20/25	Constriction, 10-20 degrees	Improved	5	Loss of vision	Posttraumatic increased intracranial pressure
13, 20, F R.E.	20/20	20/20	Constriction, 10-20 degrees	Full	5	Obscurations	Acetazolamide failure
13, 20, F L.E.	20/20	20/20	Constriction, 10-20 degrees	Full	2	Obscurations	—
14, 38, F R.E.	20/30	20/20	Increased blind spot	Full	38	Diplopia	Sixth nerve paresis, both eyes
14, 38, F L.E.	20/30	20/20	Increased blind spot	Full	37	Diplopia	—
15, 32, F R.E.	20/30	20/25	Constriction, 20-30 degrees	Full	24	Loss of vision, headaches	—
15, 32, F L.E.	20/30	20/25	Constriction, 20-30 degrees	Full	20	—	—
16, 30, F R.E.	20/50	20/20	Constriction, 20-30 degrees	Full	2	Loss of vision	Acetazolamide failure
17, 29, M R.E.	20/25	20/20	Constriction, 10-20 degrees	Mild improvement	2	Obscurations	Lithium
17, 29, M R.E.	20/25	20/20	Constriction, 20-30 degrees	Full	14	Obscurations	Reoperated on, inadequate primary operation
17, 29, M L.E.	20/25	20/20	Constriction, 10-20 degrees	Full	16	Obscurations	—
18, 28, F R.E.	20/400	20/20	Constriction, 10-20 degrees	Full	40	Loss of vision	Intracranial pressure refractory to steroids, Acetazolamide and lumbar puncture
18, 28, F L.E.	20/20	20/20	Constriction, 20-30 degrees	Full	40	Obscurations	—
19, 49, F L.E.	20/30	20/20	Constriction, 20-30 degrees	Full	25	Obscurations	Asymmetric papilledema; disk R.E., normal
19, 49, F R.E.	20/40	20/20	Constriction, 20-30 degrees	Full	2	Obscurations	Disk L.E., normal; R.E., swollen
20, 28, F R.E.	20/70	20/25	Constriction, 10-20 degrees	Improved	5	Obscurations	Second trimester of pregnancy
21, 27, F R.E.	20/20	20/20	Constriction, 20-30 degrees	Full	24	Headaches	Acetazolamide failure
21, 27, F L.E.	20/20	20/20	Constriction, 20-30 degrees	Full	24	—	—
22, 21, F R.E.	20/200	20/70	Constriction, 10-20 degrees, central scotoma	Expanded, relative scotoma	12	Visual loss	Intracranial pressure, 540 mm cerebrospinal fluid
23, 35, F R.E.	20/40	20/20	Constriction, 10-20 degrees	Full	15	Obscurations	—
24, 28, F L.E.	20/40	20/30	Constriction, 10-20 degrees	Full	2	Obscurations	Lumboperitoneal shunt failed twice
25, 40, F R.E.	20/20	20/20	Constriction, 20-30 degrees	Improved	3	Obscurations	Corticosteroid toxic, multiple lumbar punctures
26, 31, F L.E.	20/30	20/20	Constriction, 30-40 degrees	Improved	41	Obscurations	Lithium

(Continued on pg. 181)

**TABLE 1 (continued)**  
**CHARACTERISTICS OF PATIENTS WITH PSEUDOTUMOR CEREBRI AND ACUTE PAPILLEDEMA UNDERGOING OPTIC NERVE SHEATH DECOMPRESSION**

CASE NO., AGE (YRS), GENDER	VISUAL ACUITY		VISUAL FIELD		FOLLOW-UP (MOS)	PRIMARY SYMPTOMS	COMMENT
	EYE	PREOPERATIVE POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE			
26, 31, F R. E.	20/30	20/20	Constriction, 30-40 degrees	Improved	41	Obscurations	—
27, 43, M R. E.	Hand motion	20/25	Constriction, 20-30 degrees central scotoma	Full	8	Loss of vision	—
28, 24, M R. E.	20/30	20/20	Constriction, 20-30 degrees	Full	44	—	—
28, 24, M L. E.	20/30	20/20	Constriction, 20-30 degrees	Full	34	—	Minimal residual disk swelling
29, 33, F L. E.	20/25	20/20	Constriction, 20-30 degrees	Full	2	Obscurations	—
29, 33, F R. E.	20/25	20/20	Constriction, 20-30 degrees	Full	2	Obscurations	—
30, 26, F L. E.	20/25	20/20	Constriction, 10-20 degrees	Full	30	Obscurations	First trimester of pregnancy, progressive visual field decrease
30, 26, F R. E.	20/25	20/20	Constriction, 10-20 degrees	Full	30	—	—
30, 37, F R. E.	20/30	20/20	Constriction, 10-20 degrees	Full	24	Obscurations	Lithium
31, 37, F L. E.	20/40	20/25	Constriction, 10-20 degrees	Full	24	—	—
31, 32, F R. E.	20/200	20/25	Constriction, 10-20 degrees	Full	28	Obscurations	—
32, 32, F L. E.	20/40	20/20	Constriction, 10-20 degrees	Full	28	Obscurations	—
32, 32, F R. E.	20/25	20/25	Constriction, 10-20 degrees	Full	18	Obscurations	Deteriorating visual field, reoperated on
33, 25, M R. E.	20/70	20/25	Constriction, 10-20 degrees	Full	26	Loss of vision	—
33, 25, M L. E.	20/40	20/25	Constriction, 20-30 degrees	Full	6	—	—
33, 25, M R. E.	20/70	20/25	Constriction, 10-20 degrees	Full	24	Headache	Reoperated on
33, 25, M L. E.	20/70	20/25	Constriction, 10-20 degrees	Full	24	—	Reoperated on
34, 72, F L. E.	20/30	20/25	Constriction, 10-20 degrees	Full	48	—	Chronic obstructive pulmonary disease
34, 72, F R. E.	20/25	20/20	Constriction, 10-20 degrees	Full	21	—	—
34, 72, F R. E.	20/25	20/20	Constriction, 10-20 degrees	Full	10	—	—
34, 72, F R. E.	Counting fingers	Counting fingers	Constriction, 30-40 degrees, central scotoma	No improvement	17	—	Lost central vision preoperatively
35, 30, F R. E.	20/40	20/30	Constriction, 20-30 degrees	Improved residual scotoma	22	—	Systemic lupus erythematosus
35, 30, F L. E.	20/200	20/60	Constriction, 20-30 degrees, central scotoma	Improved residual constriction and scotoma	22	—	—



**TABLE 2**  
**CHARACTERISTICS AND VISUAL RESULTS OF PATIENTS UNDERGOING REPEAT OPTIC NERVE SHEATH DECOMPRESSION**

CASE NO., AGE (YRS), GENDER	EYE	VISUAL ACUITY		VISUAL FIELD		TIME, PRIMARY OPERATION TO REOPERATION (MOS)	TOTAL FOLLOW-UP (MOS)	SYMPTOMS AT INITIAL EXAMINATION
		PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE			
1, 32, F	L. E.	20/20	20/20	Constricted 20-30 degrees	Full	14	6	Obscurations, headaches
2, 28, F	L. E.	20/20	20/20	Constricted 20-30 degrees	Full	5	—	Obscurations
2, 28, F	L. E.	20/20	20/20	Constricted 20-30 degrees	Full	5	26	Obscurations
3, 31, F	R. E.	20/30	20/25	Constricted 20-30 degrees	Full	2	26	Obscurations
4, 28, M	L. E.	20/25	20/20	Constricted 20-30 degrees	Full	2	21	Obscurations
5, 32, F	L. E.	20/30	20/25	Constricted 20-30 degrees	Full	6	—	Obscurations
5, 32, F	L. E.	20/50	20/20	Constricted 20-30 degrees	Full	20	1	Obscurations
6, 29, M	R. E.	20/25	20/20	Constricted 10-20 degrees	Full	2	21	Obscurations
7, 25, M	R. E.	20/70	20/25	Constricted 10-20 degrees	Full	6	25	Obscurations
7, 25, M	L. E.	20/40	20/25	Constricted 10-20 degrees	Full	6	25	Headache, decreased visual acuity
8, 66, F	R. E.	20/25	20/20	Contracted, < 10 degrees	Full	21	—	Decreased visual acuity
8, 66, F	R. E.	Counting fingers	Counting fingers	Central scotoma	No improvement	10	17	Decreased visual acuity
9, 57, F	R. E.	Counting fingers	20/400	Central scotoma	Improved	8	18	Recurrent opticociliary shunts

compression did not have good restoration of visual function. Definitive treatment for visual loss (optic nerve sheath decompression) had been delayed in many of these patients while they underwent multiple ventriculoperitoneal and lumboperitoneal shunting procedures or an ineffective medical regimen (Table 3). Patients with papilledema may develop asymptomatic constriction of their visual fields, eventually interfering with their central vision and becoming symptomatic. It is important that patients with papilledema follow up their treatment with regular visual field testing and ophthalmic examinations to detect early deterioration of visual function. Too often patients with

papilledema and pseudotumor cerebri are referred from ophthalmologists to neurologists and neurosurgeons and do not obtain adequate ophthalmic follow-up examinations. Ophthalmologically neglected patients are those apt to develop chronic atrophic papilledema and visual loss.

Increased intracranial pressure causes visual dysfunction by compressing optic nerve fibers in the subarachnoid space of the retrobulbar optic nerve with obstruction of intra-axonal fluid mechanics. After weeks or months, nerve fiber attrition causes progressive loss of visual field.<sup>6</sup> We believe that optic nerve sheath decompression should be performed at the first

**TABLE 2 (Continued)**  
**CHARACTERISTICS AND VISUAL RESULTS OF**  
**PATIENTS UNDERGOING REPEAT OPTIC NERVE**  
**SHEATH DECOMPRESSION**

SURGICAL INDICATIONS	COMMENT
Progressive visual field loss, increased obscurations	Lithium
Decreased visual field, increased obscurations	Asymmetric papilledema, thick arachnoid
Decreased visual field, increased obscurations	—
Decreased visual field, increased obscurations	Asymmetric papilledema, thick arachnoid
Decreased visual field	Inadequate primary optic nerve sheath decompression
Decreased visual field, increased obscurations	Asymmetric papilledema, thick arachnoid
Decreased visual field, increased obscurations	Asymmetric papilledema
Decreased visual field, increased obscurations	Lithium, inadequate primary operation
Increased headache, decreased visual acuity	Mild papilledema
Increased headache, decreased visual acuity	Mild papilledema
Increased headache, decreased visual acuity	Mild papilledema
No improvement postoptic nerve sheath decompression	Mild papilledema
Recurrent optociliary shunts	Optociliary shunt resolved after surgery, chronic atrophic papilledema

objective clinical sign of progressive optic nerve dysfunction. Optic nerve sheath decompression relieves the pressure on the optic nerve axons, allowing normalization of intra-axonal fluid mechanics. Such intervention normalizes visual function in most patients with acute papilledema (Table 1). This is supported by the significant improvement in visual function ( $P = .0001$ ) documented by quantitative automated perimetry after successful optic nerve sheath decompression. Complications caused by optic nerve sheath decompression in experienced hands are minimal<sup>3-5</sup> and in this series did not cause any significant visual morbidity. However, any operation performed on

the optic nerve may potentially cause visual loss, especially when performed by inexperienced surgeons. We advise all patients undergoing optic nerve sheath decompression that the operation may cause visual loss.

Our most significant complication of optic nerve sheath decompression was late failure (13 eyes). Late failure manifests itself by recurrent obscurations or progressive deterioration of visual field after an initial postoperative improvement. After reviewing videotapes of failed operative procedures and the subsequent repeat operations, we find several reasons for optic nerve sheath decompression failure (Table 2). Early failure (several months) may result from inadequate fenestration or incision into the optic nerve sheath. This may be avoided by a more aggressive initial optic nerve sheath decompression with multiple fenestrations and incisions of the optic nerve sheath. Considering the technical difficulty inherent in repeat optic nerve sheath decompression procedures, more extensive initial operations are worth the extra time and increased risk involved. A second group of patients had asymmetric papilledema and marked thickening of their arachnoid observed at surgery. Such patients also required multiple, large fenestrations and/or incisions into their optic nerve sheaths. A third group of patients had late failure of their optic nerve sheath decompression. These orbits manifested extensive scarring and fibrosis of orbital fat throughout the retrobulbar intraconal space. Surgical landmarks were obliterated, and repeat optic nerve sheath decompression was difficult. We cannot determine which eyes may be subject to late failure, but we try to limit orbital inflammation by minimizing surgical manipulation and operating time and avoiding the use of even bipolar cautery in the intraconal space.

Despite the technical difficulties encountered in repeat optic nerve sheath decompression, it is a safe and effective method for treating patients with pseudotumor cerebri with recurrent obscurations and visual field loss at initial examination after a failed primary optic nerve sheath decompression.

Optic nerve sheath decompression is a safe and effective surgical procedure for patients with papilledema and visual loss. We advocate early surgical intervention before marked attrition of axons develops. In patients with failed primary optic nerve sheath decompression, sec-



**TABLE 3**  
**RESULTS OF OPTIC NERVE SHEATH DECOMPRESSION IN PATIENTS WITH PSEUDOMOTOR CEREBRI AND CHRONIC ATROPHIC PAPILLEDEMA**

CASE NO., AGE, (YRS), GENDER	EYE	VISUAL ACUITY		VISUAL FIELD		FOLLOW-UP (mos)	PRIMARY SYMPTOMS	COMMENT
		PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE			
1, 16, F	R. E.	20/60	20/40	< 5 degrees	5-10 degrees	8	Loss of vision	Failed corticosteroids and acetazolamide
1, 16, F	L. E.	20/60	20/40	< 5 degrees	5-10 degrees	8	—	Osteothoracic dystrophy
2, 6, M	R. E.	Hand motion	20/25	—	—	4	Loss of vision	Osteothoracic dystrophy
2, 6, M	L. E.	Hand motion	20/25	—	—	4	—	Osteothoracic dystrophy
3, 26, M	R. E.	Hand motion	Hand motion	—	—	Lost	Loss of vision	Optociliary shunts, optic atrophy
3, 26, M	L. E.	Hand motion	Hand motion	—	—	Lost	—	Visual loss on acetazolamide; noncompliant
4, 35, F	R. E.	Hand motion	Hand motion	—	—	9	Loss of vision	Corticosteroid toxic
4, 35, F	L. E.	20/200	20/200	—	—	9	—	Lumboperitoneal shunt twice
5, 53, M	L. E.	20/20	20/20	Constriction < 10-20 degrees	No improvement	6	Headache	Visual loss on acetazolamide
6, 35, F	R. E.	20/800	20/800	Constriction < 10-20 degrees	No improvement	9	—	Ventriculoperitoneal shunt failed twice
6, 35, F	L. E.	20/800	20/200	Constriction < 10-20 degrees	Improved	9	—	—
7, 42, F	L. E.	20/20	20/20	Constriction 20-30 degrees	Full	46	Headache	Acetazolamide intolerant
8, 7, F	R. E.	20/40	20/30	Constriction 20-30 degrees	Full	36	Loss of vision	Plagiocephaly
8, 7, F	L. E.	Hand motion	Hand motion	Constriction 20-30 degrees	No improvement	36	—	—
9, 22, F	R. E.	20/25	20/20	Constriction 10-20 degrees	No improvement	14	Headache	Posttraumatic
10, 55, F	R. E.	Hand motion	Hand motion	Constriction 10-20 degrees	No improvement	22	Loss vision	Optociliary shunts regressed L. E. after surgery
10, 55, F	L. E.	Hand motion	Hand motion	Constriction 10-20 degrees	No improvement	22	—	—
11, 26, F	L. E.	Hand motion	Counting fingers	Constriction 10-20 degrees	No improvement	6	Loss of vision	—
11, 26, F	R. E.	20/400	20/400	Constriction 10-20 degrees	No improvement	6	—	—
12, 33, F	L. E.	20/200	20/100	Constriction 10-20 degrees	No improvement	27	Obscurations	Lumboperitoneal shunt failed three times
13, 6, M	R. E.	20/LP	Counting fingers	—	—	3	—	—
13, 6, M	L. E.	20/30	20/30	Constriction 30 degrees	No improvement	3	Loss of vision	Lumboperitoneal shunt failed twice
14, 29, F	L. E.	20/50	20/50	Constriction 30-40 degrees	Improvement	23	—	Ventriculoperitoneal shunt failed twice
15, 39, F	L. E.	20/40	20/40	Constriction 20-30 degrees	No improvement	22	Loss of vision	Noncompliant
15, 39, F	R. E.	20/30	20/30	Constriction 20-30 degrees	No improvement	22	—	—

(Continued on pg. 185)

**TABLE 3 (Continued)**  
**RESULTS OF OPTIC NERVE SHEATH DECOMPRESSION IN PATIENTS WITH PSEUDOMOTOR CEREBRI AND CHRONIC ATROPHIC PAPILLEDEMA**

CASE NO., AGE, (YRS), GENDER	EYE	VISUAL ACUITY		VISUAL FIELD		FOLLOW-UP (mos)	PRIMARY SYMPTOMS	COMMENT
		PREOPERATIVE	POSTOPERATIVE	PREOPERATIVE	POSTOPERATIVE			
16, 33, F	L. E.	20/40	20/30	Constriction 10-20 degrees	No improvement	4	—	—
16, 33, F	R. E.	Counting fingers	Counting fingers	—	—	3	Asymptomatic	Dense aniso- metropic am- blyopia
17, 69, M	L. E.	20/40	20/30	Constriction 10-20 degrees	No improvement	17	—	—
17, 69, M	R. E.	20/40	20/30	Constriction 30-40 degrees	No improvement	17	—	Decreased optociliary shunts after surgery
18, 57, F	R. E.	Counting fingers	Counting fingers	Constriction 10-20 degrees	No improvement	8	Loss of vision	—
18, 57, F	L. E.	20/40	20/25	Constriction 30-40 degrees	Improvement	21	—	—
18, 57, F	R. E.	Counting fingers	20/400	Constriction 10-20 degrees	No improvement	13	—	Reoperate for visual field deterioration

ondary or even tertiary optic nerve sheath decompression effectively obviates obscurations and restores visual function. We believe that repeat optic nerve sheath decompression is an excellent alternative to neurosurgical shunting procedures.

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# The Effect of Topical Administration of Indomethacin on Symptoms in Corneal Scars and Edema

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We conducted a masked randomized study of 50 patients to evaluate the effect of administration of topical indomethacin 1% suspension on symptoms in corneal scars, edema, infiltrates, and erosions. Patients with symptoms (photophobia, pain, itching, burning sensation, foreign-body sensation, and tearing) were treated with topically administered indomethacin 1% or placebo and monitored for eight weeks. The severity of the complaints was rated and the scores were evaluated (Wilcoxon rank-sum test). Of the 25 patients treated with indomethacin, 21 (84%) had improvement in symptoms and the severity of each of the symptoms was significantly decreased. Of the 25 patients treated with placebo, one (4%) had improvement in symptoms without statistical change of the severity of the symptoms. However, when the placebo-treated patients received indomethacin drops, the symptoms were significantly decreased ( $P < .002$ ). This study suggests that topical administration of indomethacin 1% may reduce ocular symptoms in patients with corneal scars, edema, or erosions.

THE PROSTAGLANDINS are important mediators in the inflammatory process. Indomethacin, a noncorticosteroidal anti-inflammatory drug, inhibits the synthesis of prostaglandins during inflammation.<sup>1-3</sup> Experimental studies have shown that topical administration of indomethacin 1% suspension into the conjunctival sac reduced the amount of prostaglandin in both normal and inflamed corneas.<sup>4</sup> Systemic administration of indomethacin has also been shown

to have an analgesic effect that is independent of its anti-inflammatory activity.<sup>5</sup>

Patients with corneal scars, corneal edema, or chronic epithelial erosions as a result of previous inflammatory disease may complain of ocular discomfort or pain without obvious clinical signs of inflammation. Often these symptoms are not appreciably ameliorated after repeated treatment with low doses of topically administered corticosteroids, whereas topical administration of higher doses of corticosteroids may lead to complications.

When a chronic subclinical inflammatory process in the cornea is associated with symptoms, the use of a noncorticosteroidal anti-inflammatory analgesic may be justified.

We therefore studied the effect of topical administration of indomethacin 1% suspension on subjective symptoms in patients with corneal scars, edema, or epithelial defects of various causes.

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## Material and Methods

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A randomized double-masked controlled study of the effect of topical administration of indomethacin 1% or placebo on subjective symptoms in patients with corneal scars, edema, infiltrates, or epithelial erosions was performed in the Department of Ophthalmology, Hadassah University Hospital, Jerusalem. Fifty consecutive 18- to 80-year-old patients (30 women and 20 men) who had corneal scars, edema, infiltrates, or epithelial erosions of various causes and subjective complaints of at least six months' duration were enrolled in our study. Twenty-four of the patients had corneal scars, 18 had corneal edema (stromal or bullous keratopathy), five had epithelial erosions, and three had subepithelial infiltrates (Table 1). Each patient had one or more of the following symptoms: photophobia, pain, itching, burning sensation, foreign-body sensation, and tearing. During the preceding six months, these patients

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**TABLE 1**  
CLINICAL SIGNS OF CORNEAL DISORDERS IN THE  
STUDY POPULATION (N = 50)

CLINICAL SIGNS	NO. OF PATIENTS	CORNEAL DISORDERS
Corneal scars	24	Perforating trauma, radial keratotomy, corneal ulcer, alkali burn, herpes keratitis, Stevens-Johnson syndrome, excision of pterygium, contact lenses, trachoma, keratoconus, corneal graft
Corneal edema	18	Bullous keratopathy (aphakic, pseudophakic), corneal grafts, Fuchs' dystrophy
Epithelial erosions	5	Facial palsy, dry eyes, contact lenses
Corneal infiltrates	3	Postadenovirus, keratoconjunctivitis

had periodically received low doses of topically administered dexamethasone phosphate 0.1% (one to three drops daily), which reduced but did not relieve the discomfort in some of the patients. All the corticosteroids or the noncorticosteroidal anti-inflammatory drugs were withdrawn four weeks before the study.

Each patient underwent a complete ophthalmic examination including visual acuity, intraocular pressure by use of applanation tonometry, biomicroscopic examination of the anterior segment with a slit lamp, and direct and indirect ophthalmoscopy of the posterior segment. Schirmer test was performed in all the eyes. Corneal photography was performed before and after the study.

The severity of the subjective ophthalmic symptoms was evaluated as follows: all the studied symptoms (photophobia, pain, itching, burning, foreign-body sensation, and tearing) were presented to each patient who had to select those that fit his or her complaints. Thereafter, each patient had to rate the severity of the symptoms according to a scale of 0 to 3 (0, no symptoms; 1, mild; 2, moderate; 3, severe). In every patient, each symptom was rated separately; additionally, the total score (the average score of all the symptoms of patients at initial examination) was calculated.

Patients were treated with topically administered indomethacin 1% in aqueous suspension and placebo, which consisted of vehicle alone (Merck, Sharp and Dohme Company, Rahway, New Jersey). Twenty-five patients were treated with indomethacin 1% drops and the other 25 patients received placebo. Each patient re-

ceived the medication according to a running number of the drug whose code was known only to the company. The patients were instructed to shake the bottle before use and to apply one drop of the medication three times daily for eight weeks. Patients were examined and the subjective symptoms were rated as described at one, three, five, and eight weeks.

On conclusion of the study, the codes were disclosed and patients who had received placebo drops were switched to topically administered indomethacin 1%. Of these 25 patients, only 18 were available for additional treatment with indomethacin drops. The symptoms were rated and the drug was administered three times daily as described. Follow-up was performed at one and two weeks.

Wilcoxon rank-sum test<sup>6</sup> was used for statistical evaluation of the therapeutic effect of administration of indomethacin suspension 1% or placebo. Scores of the first and the last examinations were used for the statistical analysis.

## Results

*Indomethacin-treated patients*—Twenty-one of the 25 (84%) indomethacin-treated patients had improvement in symptoms. Nine patients (36%) were relieved of all symptoms. Twelve patients (48%) had relief of some symptoms and decrease of others but still remained symptomatic. Comparison of scores of symptoms before and after indomethacin administration showed a statistically significant decrease of the rating of each symptom and of the total score ( $P < .0004$ ; Table 2). The symptoms remained unchanged in four patients who had corneal scars (two patients), corneal edema (one patient), and presumably adenovirus-induced subepithelial infiltrates (one patient).

One patient had swelling of the eyelid after four weeks. Administration of the drug was discontinued and the scores of the previous examination were used for statistical evaluation.

*Placebo-treated patients*—Statistical evaluation of the rating of each symptom or the total scores in patients before and after administration of placebo disclosed no significant changes (Table 3). Of these 25 placebo-treated patients, only one had relief of all symptoms and two had decrease of the symptoms, but remained symptomatic. However, when at the conclusion



**TABLE 2**  
RATING OF SYMPTOMS IN INDOMETHACIN-TREATED  
GROUP BEFORE AND AFTER ADMINISTRATION OF  
INDOMETHACIN

SYMPTOM	NO. OF PATIENTS	SCORE		P VALUE
		BEFORE TREATMENT (MEAN $\pm$ S.D.)	AFTER TREATMENT (MEAN $\pm$ S.D.)	
Photophobia	24	2.58 $\pm$ .59	.54 $\pm$ .83	<.0001
Tearing	18	2.27 $\pm$ .49	.17 $\pm$ .51	<.0003
Itching	8	2.25 $\pm$ 1.04	.25 $\pm$ .46	<.0180
Burning	14	2.50 $\pm$ .76	.64 $\pm$ .84	<.0022
Pain	12	2.50 $\pm$ .67	.58 $\pm$ .90	<.0037
Foreign body	9	2.22 $\pm$ .83	.33 $\pm$ .50	<.0117
Total score	25	2.50 $\pm$ .50	.52 $\pm$ .66	<.00004

of the study 18 patients of these 25 received indomethacin for two weeks (seven patients failed to appear for the final part of the study), the rating of the symptoms showed a significant decrease as compared to the pretreatment scores (Table 4). Of these 18 patients, two had swelling of the eyelids at the first week of the administration of the drug. In these two patients administration of indomethacin was discontinued and the scores were not included in the statistical evaluation. Of the 16 remaining patients, 12 (75%) had partial or complete relief of symptoms. Eight patients (50%) remained asymptomatic and four (25%) had alleviation of some of the symptoms but still remained symptomatic. Four patients whose symptoms did not change had corneal edema (one patient), corneal scars (two patients), and

**TABLE 4**  
RATING OF SYMPTOMS IN PLACEBO-TREATED GROUP  
AFTER ADMINISTRATION OF INDOMETHACIN AFTER  
THE STUDY

SYMPTOM	NO. OF PATIENTS	SCORE		P VALUE
		BEFORE TREATMENT (MEAN $\pm$ S.D.)	AFTER TREATMENT (MEAN $\pm$ S.D.)	
Photophobia	14	2.07 $\pm$ 1.14	.64 $\pm$ 1.08	<.025
Tearing	12	2.08 $\pm$ .90	.50 $\pm$ 1.00	<.005
Itching	6	2.83 $\pm$ .41	.67 $\pm$ .82	<.027
Burning	8	2.50 $\pm$ .76	.88 $\pm$ 1.13	<.018
Pain	7	2.86 $\pm$ .38	.57 $\pm$ 1.13	<.028
Foreign body	9	2.78 $\pm$ .44	1.33 $\pm$ 1.41	<.028
Total score	16	2.40 $\pm$ .64	.71 $\pm$ .99	<.002

**TABLE 3**  
RATING OF SYMPTOMS IN PLACEBO-TREATED GROUP  
BEFORE AND AFTER ADMINISTRATION OF PLACEBO

SYMPTOM	NO. OF PATIENTS	SCORE		P VALUE
		BEFORE TREATMENT (MEAN $\pm$ S.D.)	AFTER TREATMENT (MEAN $\pm$ S.D.)	
Photophobia	22	2.64 $\pm$ .66	2.18 $\pm$ 1.02	NS*
Tearing	17	2.29 $\pm$ .85	2.12 $\pm$ .99	NS
Itching	7	2.29 $\pm$ 1.11	2.71 $\pm$ .49	NS
Burning	11	2.54 $\pm$ .69	2.54 $\pm$ .49	NS
Pain	9	2.33 $\pm$ 1.00	2.67 $\pm$ .50	NS
Foreign body	13	2.85 $\pm$ .38	2.54 $\pm$ .54	NS
Total score	25	2.51 $\pm$ .55	2.37 $\pm$ .76	NS

\*NS indicates nonsignificant.

presumably adenovirus-induced subepithelial infiltrates (one patient).

Of the total 41 patients who received indomethacin for at least two weeks, pain was decreased in 100% of the cases, and the other symptoms were reduced in 81% to 88% of the patients (Table 5).

Biomicroscopic examinations of the corneas showed no structurally visible changes, except in one patient (treated with indomethacin) who presumably had adenovirus-induced stromal infiltrate that cleared during the period of the study.

## Discussion

The major problem in our study is the bias in the evaluation of subjective symptoms such as types of pain, which are beyond absolute analysis. Numerals can be used to describe the sever-

**TABLE 5**  
IMPROVEMENT IN SYMPTOMS AFTER TWO WEEKS OF  
ADMINISTRATION OF INDOMETHACIN IN 41 PATIENTS

SYMPTOM	NO. OF PATIENTS	IMPROVEMENT IN SYMPTOM (%)
Photophobia	38	87
Itching	13	85
Pain	15	100
Burning	22	82
Tearing	30	86.6
Foreign body	16	81

ity of feelings,<sup>7</sup> but validity can only be relative and examined by empiric comparison.<sup>8</sup> For an ideal study, patients should have a chronic pain of constant severity which is expected to last at least during the study period. Our patients had long-standing symptoms including pain, burning, and foreign-body sensation and those who received placebo treatment remained symptomatic during the period of the administration of the drug. Although the examined eyes did not have visibly active inflammation, many patients scored maximal rates for the suggested symptoms. Perhaps pain and discomfort became the major focus for their interests, which led to subjectively high scoring. Furthermore, those who received placebo remained symptomatic and had persistently unchanged high scores throughout the study, whereas those who were treated with indomethacin had dramatic decrease of the scores.

It is difficult for a patient to differentiate and rate types of pain or discomfort. We therefore used the simplest method of scoring with only four grades for each symptom. In order to avoid the bias of the subjective perception of symptoms, we used a randomized double-masked technique. We used Wilcoxon rank-sum test for statistical analysis.

In this study, administration of indomethacin relieved most of the subjective symptoms in the treated eyes (21 of the 25 eyes) without clinically observed changes in the cornea or conjunctiva (except in one case). In contrast, no such effect was observed in eyes treated with placebo. However, when the placebo-treated patients were switched to indomethacin treatment after the code became known, the symptoms were relieved in 12 of the 16 (75%) cases. Presumably, prostaglandin release directly or indirectly induced some of the symptoms. Interestingly, many of our patients were previously treated with low doses of corticosteroids (two to three drops daily), but the improvement in symptoms did not justify long-term use of these drugs. Unfortunately, we did not rate the severity of symptomatic complaints before or during the use of the corticosteroids because our patients were not under study protocol at that time. Furthermore, many of the patients stopped use of the corticosteroids several months before this study began. Because all the placebo-treated patients remained symptomatically unchanged during the study, we believe that the use of the corticosteroids did not interfere with our study. Corticosteroids block both the cyclo-oxygenase and the

lipo-oxygenase pathways, whereas indomethacin affects only the cyclo-oxygenase pathway. Although we cannot compare corticosteroid and indomethacin treatments in this study, it is possible that administration of corticosteroids at low concentrations is less effective than topical administration of indomethacin in reducing the symptoms reported by our patients. One could expect greater effect if a higher dose of corticosteroids would be used because glucocorticoids express anti-inflammatory activity by means of a complex series of cellular responses among which are the inhibition of lysosomal release<sup>9,10</sup> and the decreased release of arachidonic acid from the phospholipids.<sup>11</sup>

Administration of indomethacin reduced most of the symptoms reported at initial examination. Pain was the only symptom that was relieved in all of the treated patients. Ferreira, Moncada, and Vane<sup>12</sup> reported that prostaglandins increase the sensitivity of pain receptors to other painful stimuli, but do not reduce the pain by themselves. Conversely, Juan<sup>13</sup> found that different mediators including E-type prostaglandins may stimulate peripheral nerves to induce pain. Prostaglandins differ from all other chemical mediators in that they induce a state of hyperalgesia by increasing the sensitivity of pain receptors to other painful or algescic stimuli.

Prostaglandins can increase the amount of cyclic adenosine monophosphate and ionic calcium at the nociceptor membrane and decrease the activation threshold. The result is increased central nervous system pain perception.<sup>5</sup> Drugs that block prostaglandin synthesis reduce pain because they revert a decreased pain threshold to a clinically normal pain threshold. Although these drugs are also anti-inflammatory, the analgesic effect is not necessarily related to the inflammatory response.<sup>14</sup> It is possible that administration of topical indomethacin in the cornea decreases pain by reducing the concentrations of prostaglandins that may increase the threshold of the pain and also by reducing the inflammatory response in the tissue.

The relief of symptoms such as tearing or photophobia may reflect the decreased pain sensation or reduced inflammation in the cornea. Although the lubricating effect of administration of eyedrops can contribute to the relief of the symptoms, it is most unlikely in our study because administration of eyedrops did not relieve the symptoms in the placebo group. Furthermore, patients whose symptoms had responded to placebo eyedrops did not have dry



eyes. Three patients presumably had adenovirus-induced stromal infiltrates. In one case, these infiltrates had cleared during the use of the indomethacin and did not return when the therapy was discontinued. We cannot relate this effect to the use of indomethacin. Because these infiltrates did not return after the treatment was discontinued may suggest that they would have cleared anyway as is often the case.

Eight patients (four patients from the indomethacin-treated group and four from the placebo-treated group who received indomethacin at the completion of the study) were unaffected by the administration of indomethacin. Interestingly, three of these eight patients had clinical evidence of a viral infection, two had subepithelial infiltrates after epidemic keratoconjunctivitis, and one had a history of stromal herpetic keratitis. We do not know the reason for the lack of response to indomethacin in these patients. Perhaps these eyes had a greater degree of inflammation than did the others or alternatively, an immune response took over and corticosteroids were required.

Three patients had swelling of the eyelids, which was compatible with allergic reaction and for this reason the administration of the drug was discontinued. In some patients, administration of topical indomethacin sometimes led to burning sensation for several minutes. This is not surprising because 80% of the normal patients who took part in a comfort study and received indomethacin suspension for four days had short periods of burning or stinging sensation.<sup>15</sup>

Administration of topical indomethacin appears to reduce ocular pain and discomfort in many patients with chronic corneal scars, edema, or epithelial erosions of various causes and can be tried for symptomatic relief.

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# Fitting of Aspheric High Gas-Permeable Rigid Contact Lenses to Scarred Corneas

J. H. C. Kok, M.D., F. Smulders, M.D., and C. van Mil, O.D.

Scarring of the cornea often results in an irregular corneal surface, which causes scattering in light perception. Therefore, the impaired visual acuity cannot be adequately corrected by spectacles in most cases. In this study, high oxygen-transmissible aspheric rigid lenses were fitted, with computer assistance, in 26 scarred eyes of 23 consecutive patients. In 15 of 26 eyes (57.7%), a successful fitting with good vision, no complications, and a sufficiently long wearing time was accomplished. The main lens-related complications included fluorescein-staining epithelial defects in five of 26 eyes (19.2%) and epithelial edema in two of 26 eyes (7.7%). Computer-aided fitting was of limited value because keratometer readings were not measurable in 50% of the cases. The results of this study indicate that the application of high oxygen-transmissible aspheric rigid contact lenses may obviate corneal surgery.

**S**CARRING OF THE CORNEA is often induced by trauma and keratitis. Fitting rigid contact lenses on scarred corneas has always been considered hazardous because of the irregularity of the corneal surface and fragility of the corneal epithelium. In addition, patients with scarred corneas are generally reluctant to wear a contact lens because of chronic suffering from eye disease.

Scarring of the cornea most often concerns one eye. Because the success of fitting a single healthy eye is already limited, fitting one that is diseased is extremely difficult. Conversely, the scarring of the cornea may be responsible for

gross changes in refraction, which may cause a disturbing imbalance in vision between both eyes or loss of peripheral vision. In the past, scleral lenses and rigid polymethylmethacrylate corneal lenses have been fitted to scarred corneas. These lenses often give a good visual correction. However, at the side of the scar the bearing zone of the lenses is often prominent because of the irregular surface of the cornea. This results in strong mechanical forces and obstruction of the tear flow, which may result in hypoxia. Moreover, epithelial edema increases the fragility of the cornea, which causes discomfort. For this reason, the wearing of such lenses is limited.<sup>1,2</sup>

To avoid these side effects, soft lenses or high gas-permeable rigid lenses could be fitted. Soft lenses are more comfortable, but in cases of irregular corneal surfaces, they are insufficient in their visual correction. Thus, rigid gas-permeable lenses are preferred for fitting to scarred eyes.

The most commonly fitted rigid lenses have been those with a spheric design. Since the early 1980s, however, aspheric (spherocylindrical) lenses have been introduced.<sup>3</sup> The shape of such a lens is defined by the base curve radius and the eccentricity value, which determines the amount of progressive flattening of the lens toward the periphery. The main advantage of the aspheric design is that excessive bearing at the side of the scar may be avoided by individual selection of base curve radius and flattening of the lens.

The primary aim in fitting contact lenses is to let the back surface of the lens run as parallel as possible with the cornea. The aspheric lens can be selected on the basis of the central and peripheral corneal curvature.<sup>4,5</sup> With the acquisition of the ideal materials for rigid lenses, the physiologic response to lens wear will be such that the patient will feel as if there were no lens on the eye.<sup>6</sup>

The purpose of this study was to determine whether aspheric high gas-permeable rigid

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contact lenses could be fitted successfully to scarred corneas. In addition, the usefulness of a computer-aided fitting system was assessed.

### Material and Methods

Aspheric high gas-permeable rigid lenses were fitted in 26 eyes of 23 consecutive patients (11 men and 12 women). The mean age of the patients was 50.5 years (standard deviation, 14 years; range, 32 to 77 years). The mean follow-up time was 1.8 years (standard deviation, one year; range, six months to four years).

The 26 corneal scars were caused by keratitis of different origins (phlyctenular keratitis, N = 6; herpes simplex keratitis, N = 3; herpes zoster keratitis, N = 1; measles keratitis, N = 1; and mycotic keratitis, N = 1; total, N = 12 [46.2%]); perforating trauma, N = 8 (30.8%); caustic trauma, N = 1 (3.8%); and corneal dystrophy, N = 5 (19.2%). The mean central astigmatism was 2.56 diopters (standard deviation, 2.0 diopters; range, 0 to 7.5 diopters). In one patient, it was impossible to take central keratometer readings. In 12 patients, we were able to take six keratometer readings. The mean corneal eccentricity was 0.66 (standard deviation, 0.3; range, 0.2 to 1.4).

Persecon CE (N = 14) and Quantum 92 (N = 12) aspheric (sphero-elliptical) lenses with high oxygen transmissibility were used. The Persecon CE lens is manufactured with an eccentricity of 0.45 and the Quantum lens has a variable eccentricity with a range of 0.6 to 0.9 (Table).

Fitting was performed using two central and four peripheral keratometry readings (horizontal and vertical meridian 30 degrees apart from the visual axis). These values were then used as

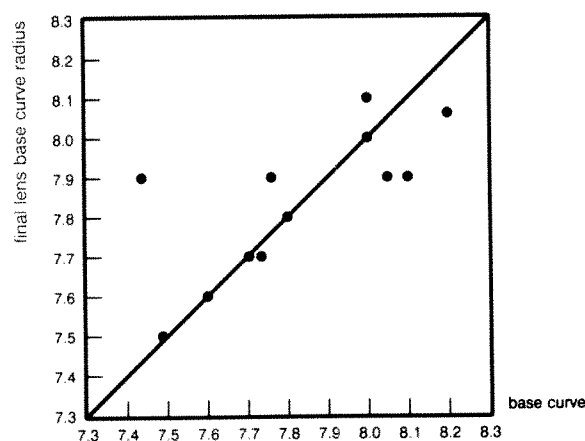


Fig. 1 (Kok, Smulders, and van Mil). Relation between the lens base curve predicted by a computer program and the base curve of the actual contact lens worn by the patient.

input for a minicomputer (Microlens, Arnhem, The Netherlands) that calculated the base curve radius and flattening of the lens according to a mathematical formula (Fig. 1).<sup>3,4</sup> With these data, the base curve radius of each contact lens was determined in combination with an eccentricity value that matched the eccentricity value of the cornea as closely as possible. Trial-and-error fitting was performed when the irregularity of the corneal surface was such that accurate keratometry readings could not be taken.

Fitting of the lenses was evaluated by examining the fluorescence pattern under the lens. The lens must exhibit a zero pressure gradient on the cornea, thereby eliminating excessive bearing areas. This is expressed in the fluorescence pattern as an even distribution of the dye, without dark (high-pressure) zones.

The score for a successful fitting was determined by good visual acuity, lack of corneal complications, and a good wearing time of at least eight hours. The computer-aided fitting procedure was considered to be successful when the computer-selected base curve radius of the lens was the same as the final base curve radius of the lens that was worn in practice. Statistical analysis was performed by use of a Mann-Whitney U-test.

TABLE  
TECHNICAL DATA OF QUANTUM AND  
PERSECON CE LENSES

	QUANTUM	PERSECON CE
Material	Fluoro-silicon copolymer (Siflufacon A)	Silicon acrylate copolymer (Pacifocon C)
Dk according to Fatt (cm <sup>2</sup> mlo <sub>2</sub> /sec ml mm Hg)	92	56
Refractive index	1.43	1.47
Eccentricity	0.6-0.9	0.45

### Results

The visual acuity achieved with the contact lens at the end of the study was compared with that obtained with spectacles before the study

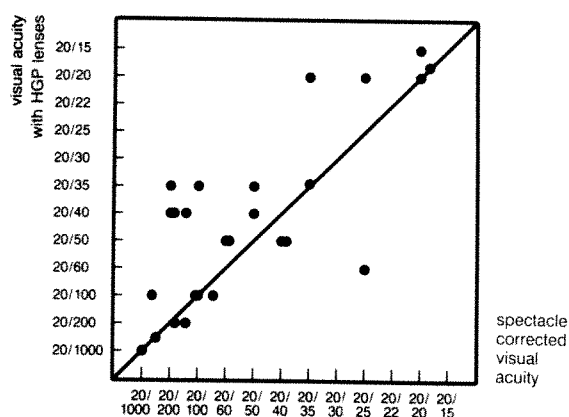


Fig. 2 (Kok, Smulders, and van Mil). Visual acuity before and after wearing contact lenses on scarred corneas. HGP indicates high gas-permeable.

(Fig. 2). Visual function with the contact lens improved in 15 of the 26 eyes (57.7%). In five eyes (19.2%), it remained the same. In six eyes (23.1%), a decrease in visual acuity was recorded. In five of these six eyes, this was related to corneal complications. Suboptimal centration of the lens was the reason for poor visual acuity in one aphakic eye. A statistically significant improvement of the visual function was observed with a  $P$  value smaller than .01 ( $P = .0086$ ).

A change in refraction may follow after scarring of the cornea. Anisometropia of more than 4 diopters existed in eight of 26 eyes (30.8%). The wearing of the lens successfully restored the binocular imbalance and peripheral visual field.

Complications, recorded with the slit lamp, were assessed in a total of ten of the 26 eyes (38.5%). These complications included fluorescein-staining epithelial defects in five (19.2%); epithelial edema in two (7.7%); recurrent herpes keratitis in two (7.7%); and progressive corneal clouding in one eye (3.8%). None of these complications resulted in elimination of patients from the study.

The wearing time may be considered as a measurement of lens tolerance. The mean wearing time was 8.5 hours, with a standard deviation of five hours and a range of zero to 15 hours. Nine of the 26 eyes (34.6%) had a wearing time of less than five hours. The lens tolerance of one patient failed because of a difficulty in understanding the lens handling instructions because of a language barrier. All of these nine eyes were considered to be failures.

Because keratometry readings are difficult to

make in scarred corneas, the computer-aided fitting system could be used in only 12 of the 26 eyes (46.2%). A statistically significant correlation between the calculated base curve radius of the lens and that of the final lens, which was worn during the study, was found. The relation coefficient was 0.784 ( $P$  value smaller than .01;  $P = .0027$ ). In 15 of the 23 patients (57.7%), a successful fitting with good vision, no complications, and sufficiently long wearing time was achieved. In this group, ten of the 15 patients (66.7%) were fitted by trial and error, and five (33.3%) were fitted by use of the computer.

## Discussion

In the past, correction of refraction in scarred corneas by fitting of scleral, polymethylmethacrylate, corneal, and low oxygen-permeable lenses has been limited by the resulting oxygen shortage under these lenses, which caused epithelial edema, epithelial defects, and limited comfort.

Aspheric gas-permeable rigid lenses have been used successfully in keratoconus,<sup>7-9</sup> in which the corneal surface is comparable to that of a scarred cornea. The success of application of these lenses for scarred corneas is somewhat lower in our study. This may be a result of lack of motivation because of the good visual acuity of the fellow eye or because of great fragility of the epithelium at the scar site.

Computer assistance in fitting scarred corneas is of limited value because reliable keratometry readings could not be performed in 50% of the cases. If keratometry readings are possible, however, then a simple computer program helps to select the correct lens in the majority of cases. Consequently, much time and effort during lens fitting will be saved.

A limited number of epikeratophakia operations have been performed after ocular trauma,<sup>10</sup> with the purpose of correcting monocular aphakia. The best-corrected postoperative visual acuity, however, was not as good as that before surgery.

Scarred corneas can be surgically treated with perforating keratoplasty. In a recent study by Doren and associates,<sup>11</sup> 41 patients underwent penetrating keratoplasty after ocular trauma. Many of the patients tried contact lenses before undergoing surgery and failed to attain good vision or comfort. This may have been



because of the design or material of the lenses used by these patients.

Scarring of the cornea is frequently accompanied by vascularization of the cornea, which has a negative influence on corneal graft survival.<sup>12</sup>

The promising results of our study indicate that the application of high oxygen-transmissible aspheric rigid contact lenses may obviate corneal surgery in a substantial number of cases.

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### OPHTHALMIC MINIATURE

Shafts of evening sunlight sloped through the garden window on to Teodor's superb white head. He was a lion of a fellow, believe me, wide browed and socratic, like a grand conductor close to genius all the time, with sculpted hands and flowing locks, and a stoop of intellectual profundity. Nobody who looked so venerable could be shallow—not even when the learned eyes appeared a mite too small for their sockets, or slipped furtively to one side in the manner of a diner in a restaurant who catches sight of a better meal passing by.

John LaCarre, *The Secret Pilgrim*  
New York, Alfred A. Knopf, 1990, p. 120

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# The Effect of Light Intensity and Dose of Dilute Pilocarpine Eyedrops on Pupillary Constriction in Healthy Subjects

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Peter D. Drummond, Ph.D.

The aim of this study was to investigate variables that influence the degree of pupillary constriction to dilute pilocarpine eyedrops in healthy control subjects. The pupillary response to 50  $\mu$ l of pilocarpine 0.0625% in darkness, dim light, and bright light was measured photographically in 15 healthy adults. Constriction to pilocarpine was greater in darkness and in dim light than in bright light, indicating that the pupillary-light reflex masked the constrictive effect of pilocarpine. In ten other subjects pupillary constriction to 50  $\mu$ l of pilocarpine 0.04%, and to 50 and 100  $\mu$ l of pilocarpine 0.0625%, was measured on separate occasions. Pupillary constriction increased in proportion to the volume and concentration of pilocarpine. Data for pupillary constriction to 50  $\mu$ l of pilocarpine 0.0625% in dim light were determined in all 25 subjects.

**A**DAPTIVE SUPERSENSITIVITY refers to the increase in sensitivity of effector tissues, such as smooth muscles, after a prolonged decrease in neural activity.<sup>1</sup> Supersensitivity to autonomic neurotransmitters is tested by measuring the tissue's response to a dose that usually induces only a small response. Assuming conditions of testing are held constant, the boundaries of clinically normal and supersensitive responses can be defined.

In ocular disturbances such as the Holmes-Adie syndrome, cholinergic supersensitivity can be tested by observing the degree of pupillary constriction to dilute pilocarpine eye-

drops.<sup>2-4</sup> This test may have some diagnostic value in distinguishing between preganglionic and postganglionic lesions of the oculomotor nerve, although this is controversial. For example, cholinergic supersensitivity is thought to develop in some patients with a chronic preganglionic oculomotor nerve lesion as a result of transsynaptic degeneration of postganglionic fibers.<sup>5</sup>

A basic problem for researchers and clinicians in this area is that the clinically normal response to dilute pilocarpine eyedrops is difficult to define, because different testing conditions and drug doses have been used in different studies. Cohen and Zakov<sup>2</sup> reported that two eyedrops of 0.0625% pilocarpine consistently induced a miosis of the tonic pupil in Holmes-Adie syndrome, but induced only a small response averaging 0.5 mm in clinically normal pupils. Unfortunately, Cohen and Zakov did not specify the volume of each eyedrop, and did not describe lighting conditions at the time of pupillary measurement. These details are important because, in bright light, the pupillary-light reflex could override the constrictive effect of pilocarpine; furthermore, the pupillary response could vary in proportion to the volume of the eyedrop. Finally, Cohen and Zakov did not report how many healthy control subjects they tested, or the range of response in these subjects.

The clinically normal pupillary response to dilute pilocarpine eyedrops was also investigated by Ramsay.<sup>3</sup> In that study, two drops of 0.05% pilocarpine, each approximately 0.04 ml, were placed in each eye. The degree of pupillary constriction after 30 minutes was measured after 30 seconds of darkness. The pupils constricted by an average of 0.54 mm, similar to the response to two drops of 0.0625% pilocarpine reported by Cohen and Zakov.<sup>2</sup>

If dilute solutions of pilocarpine do test for cholinergic supersensitivity, it is surprising that 0.05% and 0.0625% eyedrops induced that

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same degree of pupillary constriction. Room lighting may have differed in the studies of Cohen and Zakov<sup>2</sup> and Ramsay.<sup>3</sup> Alternatively, the volume of eyedrops could have differed in the two studies, thus canceling out differences in concentration.

The purpose of this study was to investigate the effects of room lighting and differences in volume and concentration of dilute pilocarpine eyedrops on pupillary constriction in healthy subjects. The reliability of individual differences in response (which may be considerable even in healthy subjects)<sup>6</sup> was also investigated. The response to administration of pilocarpine eyedrops was measured in one eye, and the degree of random fluctuation in pupil diameter over time was measured in the other eye.

### Subjects and Methods

The subjects were ten men and 15 women aged between 20 and 50 years (mean age, 32 years; standard deviation,  $\pm 10$  years). None of the subjects had a history of eye disease or of damage to cranial or autonomic nerves.

Pilocarpine eyedrops were prepared by diluting a standard 1% solution 15 times (0.0625% concentration) or 24 times (0.04% concentration) with sterile 0.9% saline solution.

The effect of light intensity on the pupillary response to 0.0625% pilocarpine eyedrops was studied in 15 subjects. Before and 30 minutes after the eyedrop was administered, both pupils were photographed simultaneously on infrared film by a camera and infrared flash in a photographic chamber.<sup>7</sup> The subject focused on a black dot attached to an illuminated screen that was 56 cm from the eyes. Two photographs were taken in darkness (0.04 lux, measured with a light meter at the position of the subject's eyes in the photographic chamber), dim light (2 lux), and moderately bright light (153.5 lux). The six photographs were taken at 30-second intervals; the lights were presented in random order. A micropipette was then used to place 50  $\mu$ l of 0.0625% pilocarpine into the conjunctival sac of one eye; the other eye served as a control. Pupils were photographed twice more at each light intensity 30 minutes later.

The effect of volume and concentration of pilocarpine eyedrops on the pupillary response was studied in ten other subjects. Pupils were photographed twice in dim light (2 lux), using

the apparatus and procedure previously described. On three occasions, each separated by at least 24 hours, 100  $\mu$ l of pilocarpine 0.0625%, 50  $\mu$ l of pilocarpine 0.0625%, or 50  $\mu$ l of pilocarpine 0.04% was placed into the conjunctival sac of one eye. The photographs were taken again 30 minutes later.

Horizontal pupil diameter was measured from the film negative, magnified six times.

### Results

Pupillary constriction to 0.0625% pilocarpine eyedrops was greater in dim light and in darkness than in bright light. The stimulated pupil constricted significantly at all three light intensities in comparison with its diameter before the eyedrop was instilled (Fig. 1). The control pupil did not change significantly from baseline value at any of the three light intensities, but increases or decreases were recorded in individual cases. After correcting for this variation, constriction to pilocarpine was greater in darkness and dim light than in bright light (paired *t*-test for pupil diameter in darkness compared with bright light,  $t[14] = 3.41$ ,  $P = .004$ ; for dim light,  $t[14] = 4.10$ ,  $P = .001$ ). The

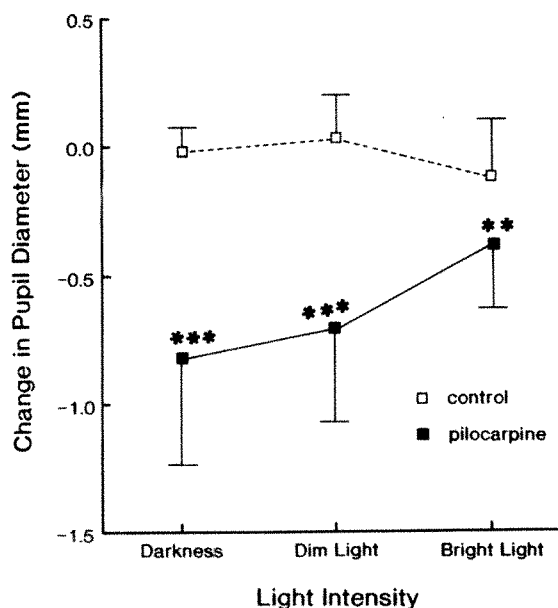


Fig. 1 (Drummond). Change in pupillary diameter 30 minutes after 50  $\mu$ l of pilocarpine 0.0625% was instilled in one eye. Negative values indicate pupillary constriction. Bars represent the 95% confidence interval. Significant change from baseline value, \*\* $P < .01$ ; \*\*\* $P < .001$ .

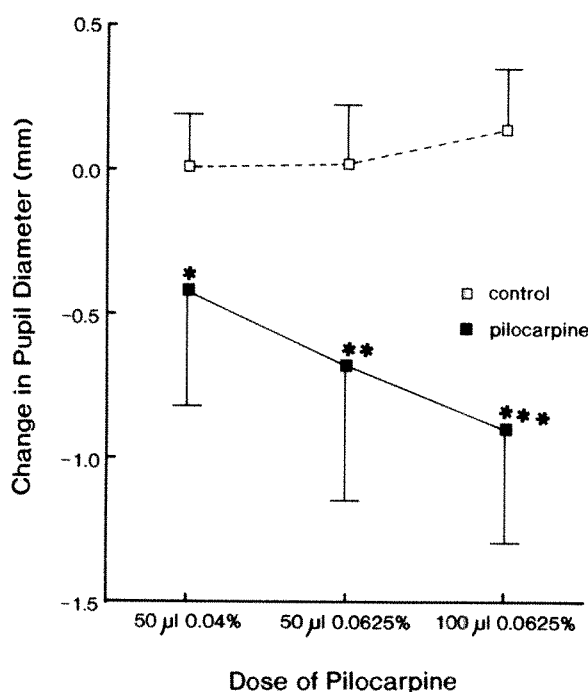


Fig. 2 (Drummond). Change in pupillary diameter 30 minutes after different doses of pilocarpine were instilled in one eye. Negative values indicate pupillary constriction, and bars represent the 95% confidence interval. Significant change from baseline value, \* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .001$ .

degree of constriction did not differ significantly between darkness and dim light.

The degree of pupillary constriction increased with both the volume and concentration of pilocarpine eyedrops (Fig. 2). After adjusting for the variation in diameter of the control pupil, constriction to 100 µl of pilocarpine 0.0625% was greater than constriction to 50 µl ( $t[9] = 3.19$ ,  $P = .01$ ). Furthermore, constriction to 50 µl of pilocarpine 0.0625% was greater than constriction to 50 µl of pilocarpine 0.04% ( $t[9] = 2.71$ ,  $P = .02$ ).

Subjects who showed the greatest response to 100 µl of pilocarpine 0.0625% also showed the greatest response to smaller doses. The correlation between the response to 50 µl of pilocarpine eyedrops and the response to 100 µl was extremely strong (Pearson's correlation coefficient = .95,  $P < .001$ ,  $n = 10$ ). The correlation between responses to these doses with the response to 0.04% pilocarpine was smaller but still significant ( $r = .73$ ,  $P = .02$  and  $r = .78$ ,  $P = .007$ , respectively;  $n = 10$ ). A response to 0.04% pilocarpine was detected in only six of ten

TABLE  
PUPILLARY CONSTRICTION TO 50 µL OF PILOCARPINE  
0.0625% IN DIM LIGHT IN 25 HEALTHY ADULTS

	PUPIL DIAMETER (MM)		PUPIL CONSTRICTION (MM)
	BEFORE EYEDROP	AFTER EYEDROP	
Mean	5.69	4.99 (5.01)*	0.70 (0.72)
Standard deviation	0.84	1.18 (1.24)	0.64 (0.61)
Minimum	4.25	2.92 (2.84)	-0.16 (0.09)
Maximum	7.08	6.83 (7.08)	1.92 (1.99)
95% Confidence interval			
Minimum	5.34	4.50 (4.50)	0.44 (0.47)
Maximum	6.04	5.48 (5.52)	0.96 (0.97)

\*Values in parentheses are corrected for variation in the control pupil.

subjects, which could account for the smaller correlations.

The response to 50 µl of pilocarpine 0.0625% in dim light was measured in all 25 subjects (Table). Most subjects' pupils constricted less than 1 mm to this dose; however, pupils constricted more than 1 mm in eight (32%) of the 25 cases (Fig. 3). Four pupils actually dilated after 0.0625% pilocarpine eyedrops. However, dilatation was probably not induced by administration of pilocarpine, because the control pupil diameter was also increased after the administration of eyedrops in each case. When corrected for variation in diameter of the control pupil, all 25 pupils showed a constrictive response to 50 µl of pilocarpine 0.0625% (Fig. 3).

Before the eyedrop was instilled, the pupils were larger in younger subjects than in older subjects (Pearson's correlation between age and pupil diameter in dim light =  $-.52$ ,  $P = .008$ ,  $n = 25$ ). This relationship is well recognized,<sup>3,8</sup> and is a result of a decrease in sympathetic tone in older subjects.<sup>9</sup> In contrast, the magnitude of pupillary constriction to 50 µl of pilocarpine 0.0625% was unrelated to the subject's age, sex, or diameter of the pupil before the eyedrop was instilled.

## Discussion

The findings indicate that lighting conditions need to be standard when measuring pupillary constriction to dilute pilocarpine eyedrops. In



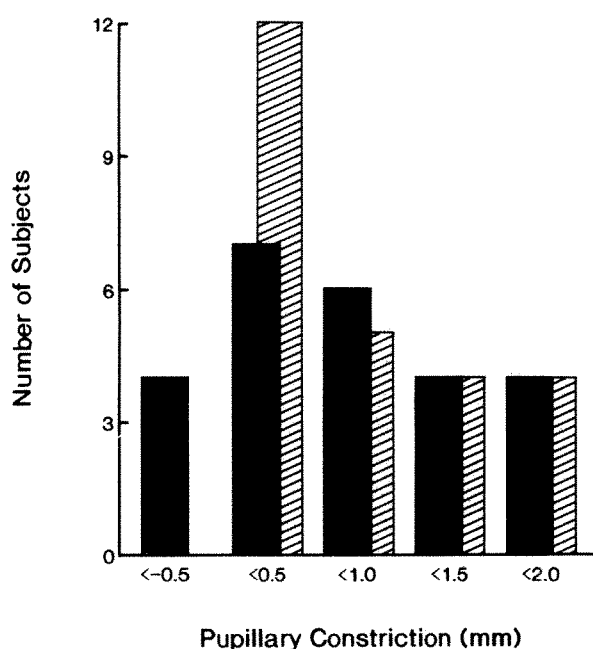


Fig. 3 (Drummond). Histogram showing the range of pupillary constriction in 25 healthy subjects to 50  $\mu$ l of pilocarpine 0.0625% instilled in one eye. Black bars represent actual change from baseline value, and hatched bars represent change from baseline value after correcting for variation in diameter of the control pupil.

bright light, constriction as a result of the pupillary-light reflex masks the effect of pilocarpine administration. Thus, pupil diameter should be measured in dim light or in darkness, before and after the eyedrops are instilled.

The volume and concentration of pilocarpine eyedrops used to test for cholinergic supersensitivity also need to be standardized. Increases in both of these variables increase pupillary constriction. These results are expected because the effect of the administration of pilocarpine eyedrops mimics the effect of administration of acetylcholine and should, therefore, show a dose-response relationship within physiologic limits. The lower limit of this relationship was reached for four of ten (40%) subjects who showed no detectable response at 0.04% concentration. The upper limit of the dose-response curve appears to be exceeded by 20  $\mu$ l of pilocarpine 0.5%, because no additional response was induced by 50  $\mu$ l at this concentration.<sup>10</sup>

In this study, pilocarpine was instilled in only one eye so that variation in diameter of the

opposite pupil could also be measured. In the group as a whole, mean diameter of the control pupil did not change consistently over time. However, increases or decreases in pupil diameter were observed in individual cases, as a result of variation in accommodative effort and alertness. These general changes in pupil diameter probably added to the response of the stimulated pupil, and thus could be considered a source of error. Removing this component of the response increased the statistical significance of comparisons between responses to different doses of pilocarpine, and to the same dose at different light intensities. Clearly, this correction cannot be made if eyedrops are instilled in both eyes. If time permits, the response of each pupil should be studied separately.

As in previous reports,<sup>6,11</sup> the degree of pupillary constriction to dilute pilocarpine eyedrops varied considerably among subjects. The size of the response was a reliable individual characteristic, and was unrelated to the subject's age, sex, or diameter of the pupil before the eyedrop was instilled. Ramsay<sup>8</sup> reported similar findings. Jacobson<sup>5</sup> found that pupils, dilated initially by hydroxyamphetamine eyedrops, showed a large constrictive response to 0.1% pilocarpine eyedrops. On the basis of this finding, Jacobson speculated that the response to dilute pilocarpine eyedrops could be greater than average in patients with preganglionic oculomotor nerve palsies merely because the affected pupil is tonically dilated. This study's finding, that pupillary constriction to dilute pilocarpine eyedrops was greater in dim light than in bright light, supports Jacobson's hypothesis. However, the lack of a relationship between basal pupil diameter and the degree of constriction to dilute pilocarpine eyedrops in dim light indicates that differences in basal diameter do not account for variation in the size of the response among healthy subjects. Differences among subjects in corneal permeability to pilocarpine eyedrops could contribute to variability in pupillary constriction; this was confirmed recently for diabetic patients under 50 years of age.<sup>12</sup>

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#### OPHTHALMIC MINIATURES

'Do hold they horning, Jan!' said Oak; and turning upon Poorgrass, 'as for you, Joseph, who do your wicked deeds in such confoundedly holy ways, you are as drunk as you can stand.'

'No, Shepherd Oak, no! Listen to reason, shepherd. All that's the matter with me is the affliction called a multiplying eye, and that's how it is I look double at you—I mean, you look double to me.'

'A multiplying eye is a very bad thing,' said Mark Clark.

'It always comes on when I have been in a public-house a little time,' said Joseph Poorgrass meekly. 'Yes; I see two of every sort, as if I were some holy man living in the times of King Noah and entering into the ark . . .'

Thomas Hardy, *Far from the Madding Crowd*  
New York, Penguin Books, 1978, pp. 347 and 348



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## Concomitant Lymphangioma and Arteriovenous Malformation of the Orbit

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Gustavo E. Coll, M.D., Robert A. Goldberg, M.D., Howard Krauss, M.D.,  
and Bronwyn J. Bateman, M.D.

An 8-year-old girl had an orbital-adnexal lymphangioma and ipsilateral orbital and middle cranial fossa arteriovenous malformations. High-resolution magnetic resonance image scanning, orbital ultrasonography, and digital subtraction angiography were used for diagnosis and preoperative assessment. Complications related to this vascular neoplasm included amblyopia, acute hemorrhage with proptosis, exposure keratitis, cosmetic deformity, and recurrent preseptal cellulitis. The girl was treated with both embolization and orbital surgery for recurrent hemorrhage and proptosis. We postulated that the coexistence of a lymphangioma and arteriovenous malformation represents an unusual and extensive maldevelopment of vascular embryogenesis.

**L**YMPHANGIOMA is an uncommon malformation that develops more frequently in the neck region than it does in the orbit.<sup>1,2</sup> It is a cystic unencapsulated lobulated mass consisting of one or more fibrous sacs containing straw-colored liquid; histologic features include thin-walled endothelial channels with loose junctions and varying stromal components. Clinically, these tumors may bleed spontaneously with a rapid increase in proptosis. The size may fluctuate with concomitant upper respiratory infections. These lesions are insensitive to irradiation and difficult to treat because the unencapsulated tumor interdigitates with normal

orbital tissue. Ocular complications are common in patients with orbital lymphangioma and include marked astigmatism, hyperopia secondary to tumor pressure on the posterior aspect of the globe, strabismus, cosmetic deformity, and compressive optic neuropathy; all predispose to amblyopia. Surgical debulking is indicated if vision is reduced progressively or the lesion is unsightly. Recently, carbon dioxide laser treatment has been used successfully to debulk the lesion.<sup>3</sup>

The association of lymphangiomas and other vascular lesions is not uncommon even in the absence of a fully expressed phacomatosis, such as the Wyburn-Mason syndrome. However, the association of an orbital lymphangioma and a congenital orbital arteriovenous malformation is uncommon. We studied a case of angiographically documented congenital orbital and middle cranial fossa arteriovenous malformations, and an ipsilateral orbital-adnexal lymphangioma.

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### Case Report

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An 8-year-old girl had been observed at birth to have a nontender mass involving the right upper and lower eyelids and cheek area; the overlying skin area was discolored. The mass increased slowly in size as the infant developed. When the patient was 1½ years of age, vision in her right eye was observed to be poor. A contact lens for this eye was fitted; glasses were prescribed for protection.

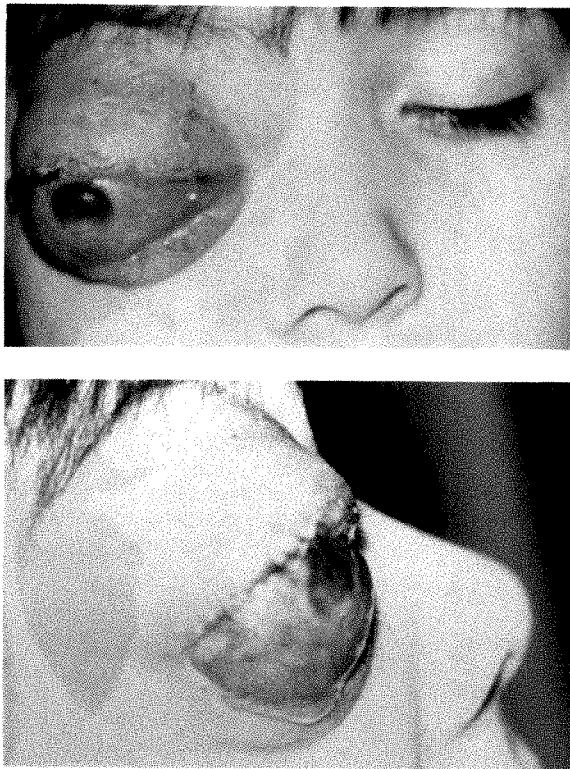
At 2½ years of age, the child had appreciably reduced vision in the right eye. A subcutaneous, nonpulsatile, compressible mass involving the right upper and lower eyelids with blepharoptosis, and proptosis with lateral displacement of the globe were observed. The right optic nerve was hyperemic. The results of the remainder of the ocular examination were unremarkable. No ocular pulsations or oral lesions

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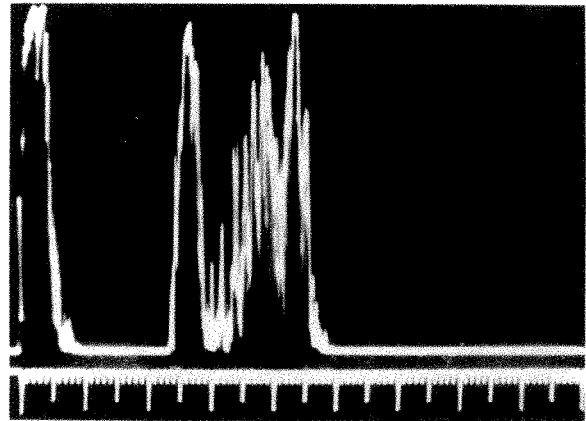


**Fig. 1** (Coll and associates). Top, anterior view; bottom, lateral view of hemorrhage within an orbital lymphangioma, causing proptosis and inferolateral displacement of the right eye.

were observed. Orbital-adnexal lymphangioma was diagnosed. Treatment of amblyopia was attempted unsuccessfully by patching the left eye.

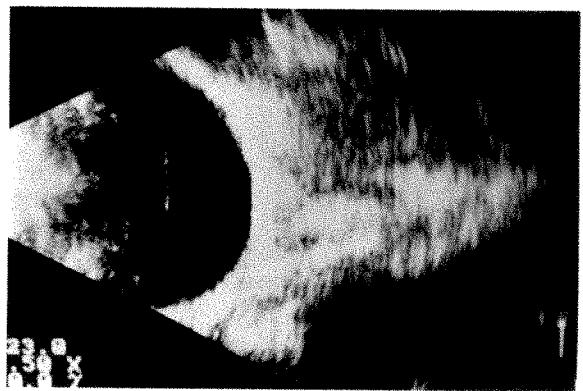
At 4 years of age, the girl's visual acuity was light perception in the right eye and 20/30 in the left eye (illiterate E). Results of pupillary examination were unremarkable and were without an afferent defect. Extraocular muscle movements were full. On external examination, the entire right upper and lower eyelids were involved with a soft subcutaneous nontender mass and blue discoloration of the overlying skin. The right eye had 4 mm of proptosis, as determined by use of Hertel exophthalmometry. The right upper eyelid had 5 mm of blepharoptosis and could only be opened manually. Eyelashes from the medial aspect of the right upper eyelid were not observed. The tumor mass also involved the right bulbar conjunctiva and eyelid margin.

At 4½ years of age, the patient had a marked increase in proptosis of the right eye. Visual acuity and results of pupillary testing were unchanged. The right eye had 13 mm of propto-



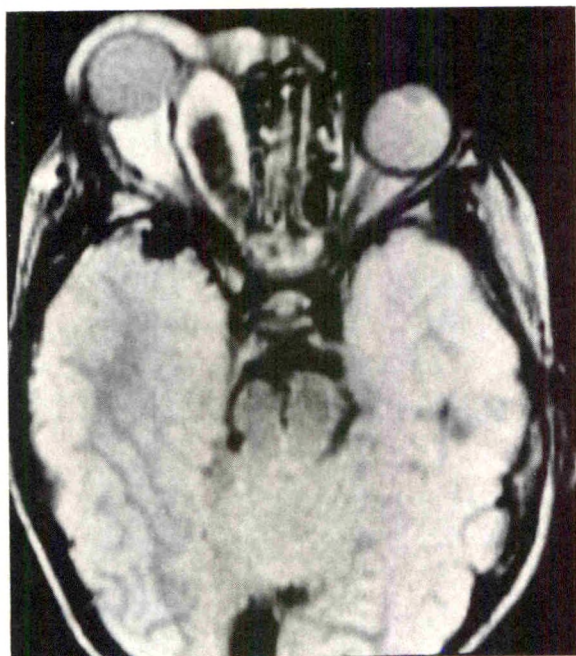
**Fig. 2** (Coll and associates). A-scan of the right orbit showing areas of low internal reflectivity with spontaneous spike motions.

sis with inferolateral displacement as determined by Hertel exophthalmometry (Fig. 1). Ultrasonography of the right orbit disclosed a

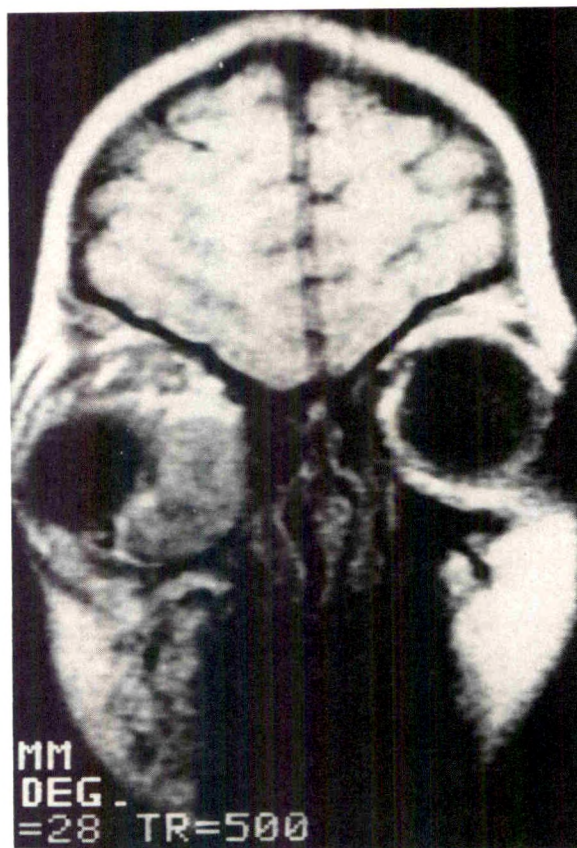


**Fig. 3** (Coll and associates). B-scan of the right orbit showing a septated, unencapsulated and round tumor located nasally with areas of hemorrhage.

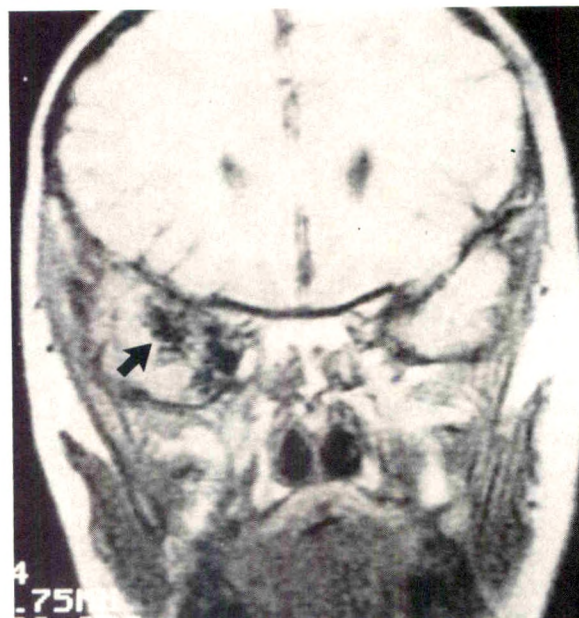




**Fig. 4** (Coll and associates). Left, Axial view. Right, Coronal view. Magnetic resonance image of the orbit showing a tumor mass involving the right eyelids and right medial orbit and displacing the eye temporally and anteriorly. The right medial orbit contains areas of hemorrhage.

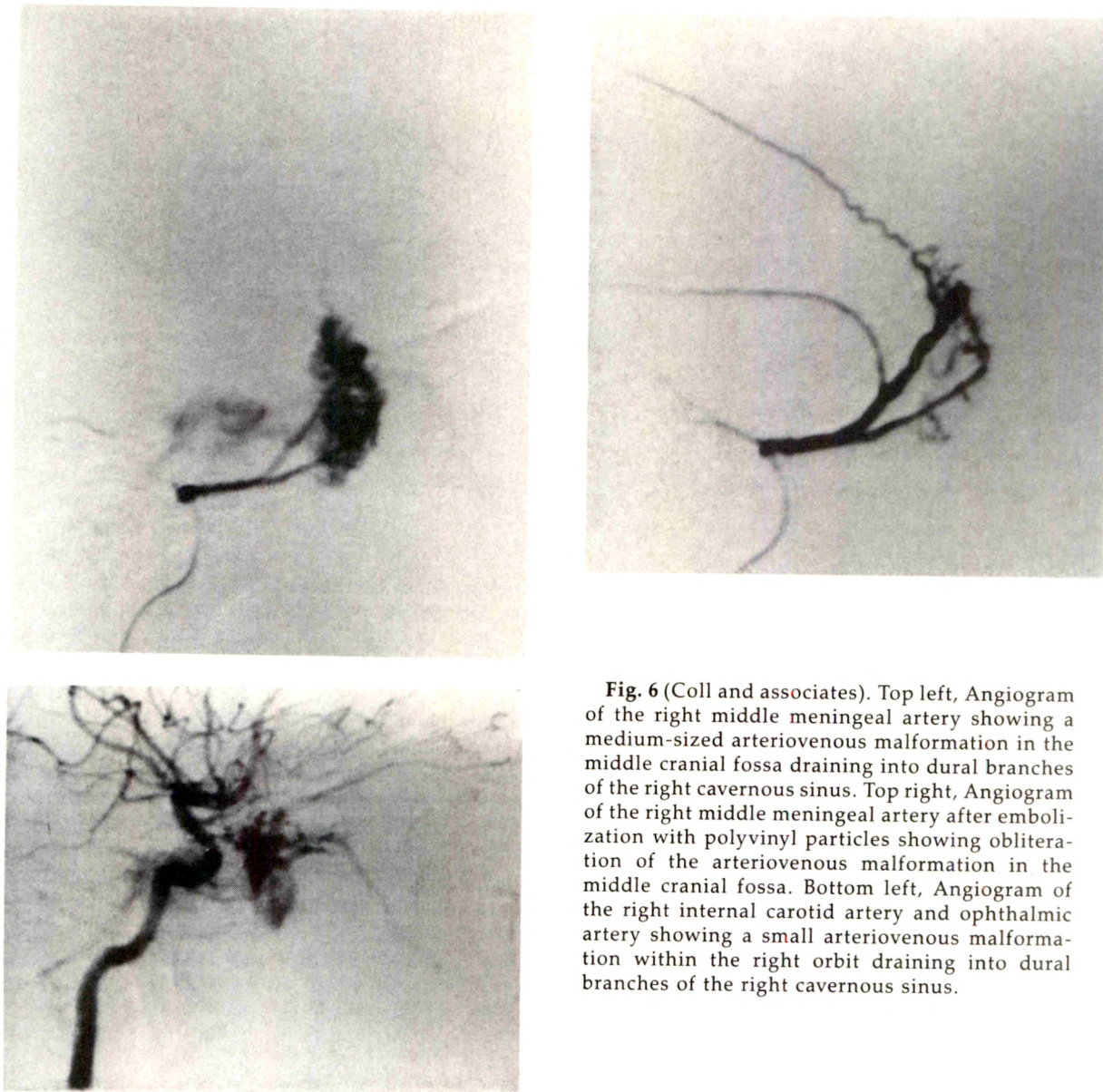


septated, unencapsulated nasal tumor with areas of hemorrhage (Figs. 2 and 3). Magnetic resonance imaging of the orbits showed a large tissue mass involving the right eyelids and the right medial orbit containing areas of probable hemorrhage and displacing the right eye temporally and anteriorly (Fig. 4). Magnetic resonance imaging of the head showed areas of low intensity corresponding to vascular regions lining the anterior aspect of the right middle cranial fossa, with increased flow in the posterior aspect of the right medial orbit (Fig. 5). Lymphangioma with two concomitant separate arteriovenous malformations was diagnosed. Selective angiography of the right middle meningeal artery originating from the external carotid artery showed a medium-sized malformation in the middle cranial fossa that drained into dural branches of the right cavernous sinus; the ophthalmic artery had a residual small malformation within the right orbit that drained into dural branches of the right cavern-



**Fig. 5** (Coll and associates). Magnetic resonance image of the head showing an arteriovenous malformation in the right temporal fossa within the middle cranial fossa (arrow).





**Fig. 6** (Coll and associates). Top left, Angiogram of the right middle meningeal artery showing a medium-sized arteriovenous malformation in the middle cranial fossa draining into dural branches of the right cavernous sinus. Top right, Angiogram of the right middle meningeal artery after embolization with polyvinyl particles showing obliteration of the arteriovenous malformation in the middle cranial fossa. Bottom left, Angiogram of the right internal carotid artery and ophthalmic artery showing a small arteriovenous malformation within the right orbit draining into dural branches of the right cavernous sinus.

ous sinus. Shortly thereafter, the malformation in the middle cranial fossa was embolized with polyvinyl alcohol particles (100  $\mu$ m) by use of guiding catheters under digital subtraction angiography (Fig. 6). Because of technical difficulties with the procedure, the ophthalmic artery could not be catheterized. Because of persistent proptosis, surgery was performed to remove the orbital arteriovenous malformation and intra-orbital hematoma. The patient underwent a surgical procedure to clamp the right ophthalmic artery, remove the orbital malformation, and drain an intraorbital hematoma. During

that procedure, it was observed that the orbital malformation was fed by many branches of the ophthalmic artery with drainage into the lateral aspect of the cavernous sinus (Fig. 7).

Several episodes of marked right proptosis developed in the ensuing years. One episode was complicated by exposure keratitis and required a temporary tarsorrhaphy. Additionally, the patient developed several episodes of facial cellulitis that required intravenous antibiotics. At the age of 6½ years, the patient underwent a second surgical procedure to remove a recurrent right orbital malformation.





**Fig. 7** (Coll and associates). Angiogram of the right internal carotid artery after excision of the right orbital arteriovenous malformation showing a surgical clip across the ophthalmic artery.

### Discussion

Lymphangioma and arteriovenous malformation in our patient were diagnosed on the basis of clinical signs at initial examination and results of imaging studies; a biopsy was not necessary. Harris and associates<sup>4</sup> reviewed 30 cases of orbital lymphangioma. In almost all cases the diagnosis was provided by imaging studies and clinical signs at initial examination. Our patient demonstrated many of the reported complications of orbital-adnexal lymphangioma including amblyopia, hemorrhagic proptosis, cosmetic deformity, and recurrent infections. The unusual coexistence of the orbital neoplasms and the clinical course necessitated multiple invasive procedures.

Whether lymphangiomas represent a venous malformation or a distinct entity is controversial. In a review of 67 cases of vascular anomalies, Wright<sup>5</sup> concluded that the majority of lesions fitting the histologic description of lymphangioma represented congenital orbital varices. Vascular connections of the lesions with the superficial veins in the orbit, demonstrated by venography, determined his view. In a review of 19 cases of orbital lymphangioma, Iliff and Green<sup>2</sup> found no abnormality of these lesions consistent with orbital varices by use of venography. They concluded that lymphangiomas represent a distinct morphologic entity.

As it is generally believed that the orbit usually contains no lymphatic channels, the origin of lymphangioma is uncertain. Jones<sup>1</sup>

suggested that in some patients, there may be embryonal lymphatic rests in the orbit. He demonstrated in animals that india ink injected into the extracellular space of the orbit appeared in the cervical lymph nodes. Many orbital lymphangiomas have anterior eyelid and conjunctival connections that may be the site of origin. Jakobiec and Font<sup>6</sup> believed that lymphangiomas may represent a vascular anlage that was misdirected during embryonic development. Rootman and associates<sup>7</sup> suggested that orbital lymphangioma is a developmental anomaly that is a result of sequestration and failure to communicate with the lymphatic system. The fundamental differentiation of this vascular neoplasm should be determined on the basis of the lack of communication with the systemic circulation. Furthermore, they suggest that the histopathologic features of orbital lymphangioma parallel the histologic findings of similar lesions in the head and neck. Therefore, orbital lymphangiomas should be classified as tumors of lymphangiomatous origin.

The stages of differentiation and maturation in vascular embryogenesis provide some basis for understanding the origin of lymphangiomas, as it conforms to the arrest of a particular embryonic development. The capillary network stage is an embryologic development of the mesenchymal primordia. With further differentiation, these primitive vessels penetrate deeper into the subcutaneous layer.<sup>8</sup> The next stage of differentiation, retiform, is characterized by the establishment of venous, arterial, and capillary systems. In the final stage of development, maturation of venous and lymphatic systems predominates; aberrations in the progressions of this stage result in lymphangiomas.<sup>9,10</sup>

If vascular tumors are caused by aberrations during vascular embryogenesis, one would expect to find different forms of vascular tumors coexisting in the same individual. In a study by Formon, Luessenhop, and Limaye,<sup>11</sup> five of 25 patients with angiographically documented congenital arteriovenous malformations of the head and neck had associated vascular malformations of the eye. Scavone and associates<sup>12</sup> reported a case of a patient with a large congenital intracranial arteriovenous malformation and a facial lymphangioma.

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#### OPHTHALMIC MINIATURE

A lake is the landscape's most beautiful and expressive feature. It is earth's eye; looking into which the beholder measures the depth of his own nature. The fluviatile trees next [to] the shore are the slender eyelashes which fringe it, and the wooded hills and cliffs around are its overhanging brows.

Henry D. Thoreau, *Walden*  
Princeton, Princeton University Press, 1971, p. 186



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## EDITORIALS

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### Human Immunodeficiency Virus, Herpes Zoster, and the Retina

Robert B. Nussenblatt and Alan G. Palestine

The list of ocular complications associated with the acquired immunodeficiency syndrome (AIDS) seems to be growing continuously. Slow progress has been made in methods to treat patients and prolong life. However, the underlying immunosuppression caused by the human immunodeficiency virus is not reversible. As clinicians, we will apparently be continuously challenged with new clinical entities that will require proper identification and appropriate therapy.

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See also p. 119

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There are several developments of clinical disease in patients with AIDS. One is the increased incidence of a relatively rare disease such as cytomegalovirus retinitis, which behaves similarly to the disease seen in patients without AIDS. Another is the emergence of a new disease such as *Pneumocystis carinii* chorioiditis, which was not seen before the AIDS epidemic, and is largely related to the attempts to prevent pneumocystis pneumonia with aro-

solized pentamidine. Lastly is the development of infections that occur in patients without AIDS, but are clinically different in the patient with AIDS.

In the past two years, a disease attributable to herpes zoster infection of the eye, which occurs only in immunocompromised individuals, has appeared. Superficially, it appears to be similar to acute retinal necrosis, but there are a variety of important distinctions that should be made. This disease fits into the category of diseases that occur in patients with AIDS, which are clinically different from those seen in patients without AIDS.

The disorder seems to progress rapidly and to be associated with little or no intraocular inflammation. The peripheral retinal vasculature is not notably affected in the early stages. A cherry-red spot with deep white retinal lesions is combined with the relentless development of atrophic or necrotic retina. There is a propensity for involvement of the optic nerve and chorioid. The cherry-red spot may be the result of central artery occlusion rather than diffuse ede-

ma. This has been observed in two cases of herpes zoster cerebral vasculitis.

Elsewhere in this issue, Margolis and associates take the isolated case reports of Forster and associates<sup>1</sup> as well as Jabs and associates<sup>2</sup> to that of a new entity. They raise important questions. Why does herpes zoster manifest itself in the eye in this new fashion? How is this new ocular disease mediated? AIDS patients who develop this disease are markedly immunosuppressed, which is reflective of the concomitant cytomegalovirus retinitis in some. There is minimal ocular inflammation in all patients. An augmented B-cell response is known to occur in patients with AIDS and this may induce an immune complex-mediated response to the proliferation of the virus. An additional possibility is a change in the thromboelastographic clotting mechanisms induced by herpes zoster, as was described to occur in AIDS patients by Murchison, Deutsch, and Goldstick.<sup>3</sup>

Clinical diagnoses in ophthalmology are based upon observational data, often without confirming tests. Whenever the clinical findings appear atypical, it is important to be aware of the possibility that a new disease may be present. This is particularly true in patients with AIDS because of the evolving nature of the disease. The report of Margolis and associates emphasizes the need for clinical and pathologic correlations before the cause of a disease process can be identified. This need has been emphasized many times in the last decade in

diseases such as pneumocystis choroiditis and acute retinal necrosis. Without a pathologic confirmation of the infectious organism, we may speculate forever as to the cause and hence the appropriate therapy.

The proper treatment of this disease remains elusive. An underlying concern is that once the clinical manifestations appear, it may be too late to save useful vision. The ocular complications of AIDS have put us on an uncharted road. We clearly have not seen the end of the journey.

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## Penicillin: 1929-1991

Frank W. Newell

A recent news item in the *British Journal of Ophthalmology* told of an exhibit at the Divinity School, Bodleian Library, Oxford University: "Penicillin 50: Oxford Fights Disease." At Oxford, Ernst Chain and his coworkers first concentrated the antimicrobial component of penicillin, and Howard Florey and his group described the first clinical trial.

The story of penicillin began with Alexander Fleming in 1928 at St. Mary's Hospital, London. As is now well known, Fleming observed inhibition of the growth of a culture of *Staphylococcus aureus* by a mold that contaminated the culture. His 1929 article, "On the antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of *B. influenzae*," is a model scientific report. He

made clear that the production of this antibacterial substance was not common to all molds or to all species of *Penicillium*. Fleming, though, apparently presumed that penicillin would be no better than flavine in the treatment of infected wounds, and thus failed to exploit the studies. One of his assistants, incidentally, was the ophthalmologist Frederick Ridley, who had worked with Fleming on lysozyme from tears, and who subsequently concentrated, but did not report the isolation of a crude active antibiotic. Ridley left Fleming's laboratory in 1932 to devote himself fully to ophthalmology.

Nearly forgotten in the story of antibiotics is the work of René Dubos, working in 1938 at the Rockefeller Institute after a long career at Rutgers University. After he emigrated to the Unit-



ed States from France, he sought bactericidal agents in bacteria, but the agents he isolated caused severe renal toxicity. It was bad luck that he had not sought agents in fungi or in the Actinomycetales, for bacteria have proven to be a poor choice. Only bacitracin, derived from bacteria, has been clinically useful. The 1940 paper of Ernst Chain and Howard Florey described their partial purification of the active inhibitory substances extracted from cultures of *P. notatum*. They credit the earlier studies of Dubos and Fleming.

The August 16, 1941, issue of *Lancet* described the first therapeutic trials using penicillin. The first patient, a 43-year-old man with suppuration of the face, scalp, and both orbits, markedly improved after five days of intrave-

nous penicillin treatment. His treatment, however, exhausted the entire supply of penicillin and the patient died. Subsequently, three patients with conjunctivitis and one patient with a corneal ulcer were treated with topical penicillin and all improved.

Even before the clinical report appeared in 1941, the international chemical industries had initiated studies concerning the commercial production of penicillin. On June 27, 1941, Florey and Norman Headley of Oxford, who had supervised the purification of penicillin, travelled to the United States to assist in wide-scale production of the antibiotic. By March 1944, 406 billion units a month were being produced, and the management of infectious disease was forever changed.

#### OPHTHALMIC MINIATURE

Descartes asserted that motion was put into the universe by God and passed from particle to particle. The human body was a machine within which the mind was a separate essence. Light was composed of tiny corpuscles of various sizes that impinged on the nerves of the retina, carrying images by way of the pineal gland to the unextended mind. Even animals were little machines that could be experimented on without feeling pain.

Carolyn Merchant, *Ecological Revolutions*  
Chapel Hill, University of North Carolina Press, 1989, p. 127

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## LETTERS TO THE JOURNAL

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### Inferior Rectus Muscle Palsy After Retrobulbar Anesthesia for Cataract Surgery

Jan-Tjeerd H. N. de Faber, M.D.,  
and Gunter K. von Noorden, M.D.

Cullen Eye Institute, Baylor College of Medicine, and Ophthalmology Service, Texas Children's Hospital. This study was supported in part by a Nato-Science Fellowship from The Netherlands Organization for Scientific Research, Stichting HOF, The Netherlands (Dr. de Faber), and the National Children's Eye Care Foundation.

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Isolated inferior rectus muscle paralysis is an infrequently reported eye muscle problem. The cause is congenital, traumatic, myasthenic, vascular, and idiopathic.<sup>1</sup> We treated a patient with iatrogenic inferior rectus muscle paresis after cataract surgery.

A 74-year-old man was referred to us because of constant diplopia after extracapsular cataract surgery in the right eye under local retrobulbar anesthesia with implantation of an intraocular lens four months previously. At the same time, medial and lateral pterygia were excised from the right eye. His left eye was pseudophakic after an uncomplicated extracapsular cataract extraction with implantation of an intraocular lens under retrobulbar anesthesia and argon laser photocoagulation of an asymptomatic peripheral retinal break two years previously. His medical history included a myocardial infarction,

prostatitis, and medically controlled hypertension.

The patient stated that the retrobulbar injection in his right orbit was extremely painful. Immediately after surgery he felt numbness of his right infraorbital region and noted blepharoptosis of the right upper eyelid. After two weeks the blepharoptosis subsided, and the patient noticed diplopia and a constant hyperopia of the right eye.

According to the operative report, 6 ml of 0.75% bupivacaine hydrochloride was injected retrobulbarly one hour before the surgery. The needle was inserted into the inferotemporal right lower eyelid, pointing to the apex of the orbit, while the patient was directed to elevate and adduct the eye. A Honan balloon was applied to decrease the intraocular pressure. A 7-0 silk bridle suture was placed through the insertion of the superior rectus muscle. The cataract surgery was uncomplicated, and the pterygia excision proceeded without difficulty.

Upon examination, best-corrected visual acuity was R.E.: 20/30 with refraction of  $-3.00 + 0.50 \times 125$  and L.E.: 20/20 with refraction of plano  $+ 0.75 \times 155$ . The right pupil was 4 mm in size, moderately reactive to light, and moderately reactive to near with no afferent pupillary defect; the left pupil was 3 mm in size, markedly reactive to light, and moderately reactive to near with no afferent pupillary defect. Slit-lamp examination was consistent with bilateral pseudophakia. Intraocular pressure was 10 mm Hg in each eye, and the visual fields were within normal limits to three-step con-

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frontation. Results of ophthalmoscopy were normal in the right eye and showed an old peripheral retinal break surrounded by photocoagulation scars in the left eye. Medical examination, including thyroid studies and neurologic examination, demonstrated no abnormalities.

Orthoptic examination showed an exotropia of 10 prism diopters with a right hypertropia of 40 prism diopters at distance and an exotropia of 16 prism diopters with a right hypertropia of 50 prism diopters at near as determined with the prism cover test in primary position while the patient was wearing his spectacles. The right hypertropia was highly incomitant and measured up to 50 prism diopters with the eyes elevated in right gaze contrasted with 25 prism diopters with the eyes depressed in left gaze. Ductions and versions showed an excess of elevation and restriction of depression of the right eye in primary position and abduction (Figure). The Bielschowsky head tilt test was unequivocal. The forced duction test showed restriction on attempts to depress the right eye. The right eye showed a floating saccade in the direction of action of the right inferior rectus muscle, which clearly indicated a palsy of this muscle.

We concluded that this patient had a right inferior rectus muscle palsy with rapid onset of secondary contracture of the unopposed ipsilateral superior rectus muscle. We suspected injury of the inferior rectus muscle from the retrobulbar injection but considered also fibro-

sis of the superior rectus muscle from a bridle-suture injury as possible causes.

Six months after the cataract extraction, the patient underwent surgical correction of his right hypertropia. During surgery the superior rectus muscle was inspected up to 12 mm posterior of its insertion and found to be normal without any scarring or other evidence of an intramuscular hemorrhage from the bridle suture. The forced duction test became negative after the superior rectus muscle had been detached from its original insertion, which indicated that this muscle had become tight after paralysis of its antagonist. Surgery consisted of a 7-mm recession of the right superior rectus muscle with a conjunctival recession, combined with a 4.5-mm resection of the right inferior rectus muscle. Three months postoperatively the patient showed a right hypertropia of only 5 prism diopters at near and distance, which increased to 10 prism diopters in right gaze. The patient was able to fuse with a slight chin elevation and had no diplopia in primary position.

Transient strabismus and blepharoptosis are fairly common and benign complications of retrobulbar anesthesia. Permanent strabismus, however, is rare.<sup>2</sup> Inferior rectus muscle paralysis in our patient can be explained by either direct trauma from the injection needle to the nerve of the inferior rectus muscle,<sup>3,4</sup> which enters the muscle in its posterior one third, or by myotoxicity of bupivacaine hydrochloride.<sup>5</sup>



**Figure** (de Faber and von Noorden). Versions in the nine diagnostic positions show an incomitant right hypertropia of 50 prism diopters in right gaze with the eyes elevated contrasted with only 25 prism diopters in left gaze with the eyes depressed.

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### Measurement of the Radius of Corneal Curvature With the Maloney Surgical Keratometer

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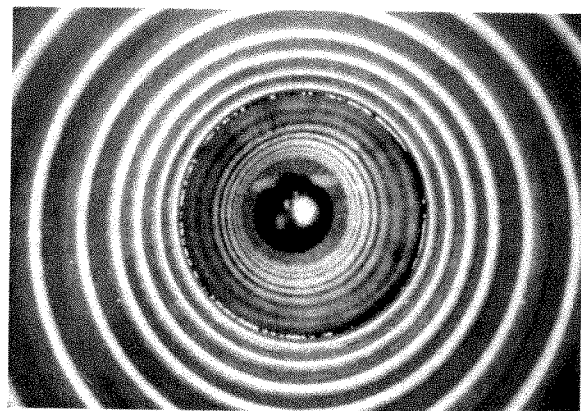
*Inquiries to Hiromasa Igarashi, M.D., Department of Ophthalmology, Asahikawa Medical College, 4-5, Nishikagura, Asahikawa 078, Japan.*

Because measuring the radius of corneal curvature in infants is sometimes difficult using an ophthalmometer and a photokeratometer, we sought an alternate method for determining the base curve when prescribing contact lenses for infants after congenital cataract surgery. The surgical keratometer developed by Maloney (Katena Products Inc., Denville, NJ) can project Placido's disk onto the cornea during surgery; the imagery then can be recorded on film or videotape.<sup>1,2</sup> If the image of Placido's disk can be analyzed in the same way as with the photokeratometer,<sup>3,4</sup> the radius of corneal curvature can be determined without using an ophthalmometer or photokeratometer. We used a photokeratometer-based system to analyze Placido's disk projected by the surgical keratometer onto the corneas of 39 eyes of 20 healthy adults (age range, 19 to 26 years; average age, 22.3

years). We then evaluated the accuracy of this method.

To obtain control data, the radii of corneal curvature also were measured in the same 39 eyes with an ophthalmometer. With the subjects in the supine position, 0.4% benoxinate hydrochloride drops were administered, and a Barraquer speculum was fitted. The surgical microscope was adjusted so that the cornea was centered in the visual field. The surgical keratometer that projected Placido's disk also was maintained in a fixed position over the cornea. When the disk projection was uniformly positioned over the corneal surface, the area was photographed (Figure). The projections of Placido's disk were traced on the photographs with black-and-white outliner pens, and an analysis was performed with the photokeratometer-based corneal shape analysis unit and the PHORM 100 corneal shape analysis software system (Suncontact, Kyoto, Japan). The results then were compared with those obtained using the ophthalmometer.

In 15 of the 39 subjects (38%), deviation in the value of the average radius of curvature was within 0.1 mm; in 27 subjects (69%), deviation was within 0.2 mm; and in 31 subjects (79%), deviation was within 0.3 mm. In 14 of the 39 subjects (36%), the error range of the flattest principal meridian was within 0.1 mm; in 25 subjects (64%), the range was within 0.2 mm; and in 31 subjects (79%), the range was within 0.3 mm. In cases in which the degree of corneal astigmatism was 1 diopter or more, the deviation tended to become larger. When the astigmatism was 1 diopter or less, however, the range of deviation was within 0.3 mm in 28 of 30 eyes (93%). Thus, based on these results our



**Figure** (Igarashi and associates). Placido's disk projected by the surgical keratometer.



method of determining the radius of corneal curvature seems to be a practical alternative for determining the base curve without using an ophthalmometer or photokeratometer.

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### Risk of Missing Angle Neovascularization by Omitting Screening Gonioscopy in Patients With Diabetes Mellitus

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The value of screening gonioscopy for detecting angle neovascularization in patients with diabetes mellitus is controversial. Some reports emphasize its importance based on cases with angle neovascularization before pupillary margin neovascularization.<sup>1-3</sup> Wand and associates,<sup>4</sup> however, found that pupillary margin neovascularization always preceded angle neovascularization, which implies that one need only perform careful slit-lamp biomicroscopy to detect anterior segment neovascularization.

To attempt to clarify this matter, I examined 310 undilated eyes in 155 patients with diabetes mellitus first with high-power, slit-lamp biomicroscopy and then with a gonioscope. Of 310 eyes, 20 eyes had both angle and pupillary margin neovascularization, 44 eyes had pupillary margin neovascularization without angle

involvement, but no eye had angle neovascularization without pupillary margin involvement.

Detecting angle neovascularization is important in patients with diabetes mellitus to prevent progression to neovascular glaucoma by treatment with laser panretinal photocoagulation. These data support the conclusion that screening gonioscopy is not necessary if careful, high-power, slit-lamp examination discloses no pupillary margin neovascularization. Conversely, presence of any pupillary margin neovascularization should prompt careful gonioscopy, since many of these patients will have angle neovascularization and need treatment. These observations apply only in patients with diabetes mellitus and should not be extended to other causes of anterior segment neovascularization, such as central retinal vein occlusion.

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### A Comparison of the Size of the Burn Produced by Rodenstock and Goldmann Contact Lenses

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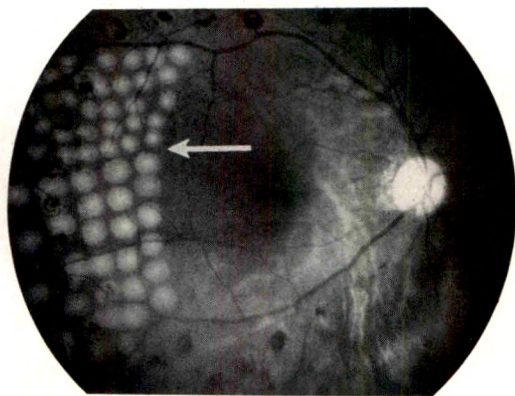
The beneficial effects of panretinal photocoagulation for proliferative diabetic retinopathy

have been well documented.<sup>1,2</sup> The two contact lenses commonly used for panretinal photocoagulation, the Goldmann three-mirror and the Rodenstock panfunduscope lens, produce burns of considerably different sizes, though clinical judgments vary on the resulting difference.

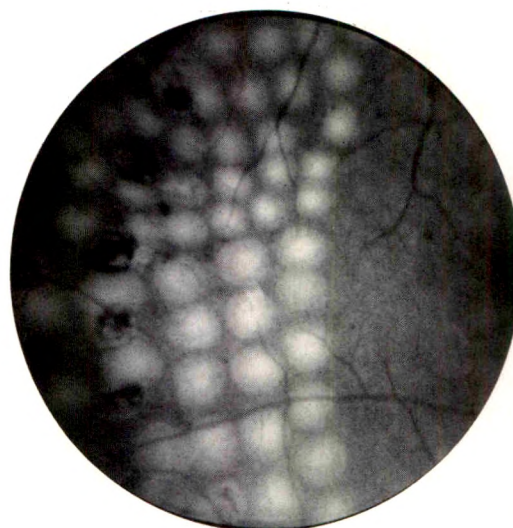
Barr<sup>3</sup> reported the mean diameter of 500- $\mu\text{m}$  argon laser burns to be 490  $\mu\text{m}$  when placed with a Goldmann lens, and 810  $\mu\text{m}$  when placed with a Rodenstock lens. He was estimating the maximum number of argon laser burns in a histopathologic study of ten autopsy eyes.

To evaluate the amount of treatment necessary for various stages of proliferative diabetic retinopathy, we sought our own measurements for the magnification of the burn size produced by the Rodenstock lens and compared it to the Goldmann lens. Ten eyes in ten patients received approximately 40 contiguous 500- $\mu\text{m}$  burns placed with both a Goldmann and Rodenstock lens, using an argon green laser. Fundus photographs were obtained immediately after this brief treatment along with a description by the surgeon of the location of burn application (Fig. 1). Panretinal photocoagulation was then completed. The photographs were subsequently enlarged and duplicated (Fig. 2).

Computer perimetry and planimetry were used to provide a value for the magnification of the laser burn size of the Rodenstock lens compared with the Goldmann lens. The software was standardized by using a figure of known dimensions, and the burn area and circumference were reproduced with an error of 2%. The



**Fig. 1** (Reddy, Zamora, and Olk). Forty contiguous 500- $\mu\text{m}$  burns were placed with a Goldmann contact lens (above arrow) and a Rodenstock contact lens (below arrow).



**Fig. 2** (Reddy, Zamora, and Olk). The fundus photograph of treatment was enlarged by using high contrast black and white film.

photographic enlargements were placed securely on a digitizing pad, and the burns were traced with a vertically placed digitizing pen. Three continuous parametric tracings per burn were made. The software provided a graphic screen representation of the tracing with numeric values of area and circumference.

Two methods were used to calculate the diameter of the burns. The first method involved dividing the circumference by  $\pi$ , and the second method involved doubling the square root of the area divided by  $\pi$ . The relative diameters were then factored and multiplied by 500  $\mu\text{m}$ , the size of the burn obtained with the Goldmann lens. The first method yielded a value of  $655 \pm 20 \mu\text{m}$  as a diameter of a Rodenstock burn, and the second method yielded a value of  $672 \pm 22 \mu\text{m}$ , thus a cumulative average of  $668 \pm 22 \mu\text{m}$ . This is in marked contrast to Barr's findings of 810  $\mu\text{m}$ . Although variation in burn size may result from the operator's habits and accommodation, astigmatism induced by the contact lens, or the depth of focus of the observation system,<sup>4</sup> these factors were controlled in our study by having only one of us (R.J.O.) perform the photocoagulation with the identical system in each patient.

Previous studies of incremental panretinal photocoagulation have relied upon Barr's measurements to provide a factor for converting a Rodenstock burn to a Goldmann equivalent. Previous calculations of total retina photocoagulated may be exaggerated since Barr's



figures indicated that the Rodenstock lens produces a magnification of 2.6 times the area of a Goldmann burn and our study showed a magnification of only 1.8 times. These measurements may be important in estimating the amount of panretinal photocoagulation treatment necessary to cause a regression of neovascularization in patients with proliferative diabetic retinopathy.

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### The Evaluation of the Kodak Surecell Test for the Detection of Ocular Herpes Simplex Virus

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Lisa M. Karenchak, B.S.,  
and Robert C. Arffa, M.D.

The Charles T. Campbell Ophthalmic Microbiology Laboratory, The Eye and Ear Institute of Pittsburgh, and Department of Ophthalmology, University of Pittsburgh. This study was supported by The Charles T. Campbell Foundation, The Eye and Ear Hospital and Institute of Pittsburgh, and Research to Prevent Blindness, Inc.

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A new 15-minute, self-contained test kit (Kodak Surecell, Eastman Kodak Company, Rochester, NY) has been developed to detect herpes simplex virus from genital and rectal samples.<sup>1</sup> This test could be perfectly suited for the ophthalmic office practice.

We evaluated the Kodak Surecell by using ocular clinical samples collected in chlamydia transport medium (Bartels, Bellevue, Washington) from the following: 22 herpes simplex virus culture-positive corneal or conjunctival samples; five adenovirus culture-positive conjunctival samples; and ten samples from normal conjunctivae. Six ocular specimens collected on swabs provided in the Kodak Surecell kit from patients with culture-positive herpes simplex virus disease were also tested. Of the herpes simplex virus culture-positive samples tested, 19 of 22 (86%) were from patients in whom the herpes simplex virus infection was both diagnosed and treated after the initial slit-lamp examination. A clinical herpes simplex virus stock isolate was serially diluted and tested with the Kodak Surecell to determine the minimum amount of virus that could be detected.

The sensitivity, specificity, positive predictive value, and negative predictive values of the Kodak Surecell were 27% (six of 22), 80% (12 of 15), 66% (six of nine), and 43% (12 of 28), respectively. Collecting ocular specimens on the swabs provided did not increase the test sensitivity (0%, 0 of six). The test efficiency was 48% (18 of 37). Slit-lamp examination (16 of 22) was significantly ( $P = .001$ ) more sensitive in diagnosing herpes simplex virus disease than the Kodak Surecell (six of 22).

The minimum amount of virus detected by the Kodak Surecell was  $1.05 \times 10^5$  plaque-forming units. This is relatively poor detection when compared to Herpcheck (DuPont, Wilmington, Delaware) ( $2 \times 10^2$ ).<sup>2</sup> Further evidence that the Kodak Surecell requires a large amount of antigen to test positive is that in cell culture a 30% to 40% monolayer involvement is necessary for the Kodak Surecell to detect herpes simplex virus antigen.

We recommend that although the Kodak Surecell is a rapid and simple test for detecting herpes simplex virus antigen, it would not be useful for the routine detection of herpes simplex virus antigen in ocular clinical specimens because of its low efficiency.

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## Bone Erosion in Nasolacrimal Duct Obstruction

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Department of Ophthalmology, Kaplan Hospital, Rehovot (Dr. Levartovsky); and Department of Otolaryngology, Tel Aviv University, Ramat Aviv (Dr. Sade).

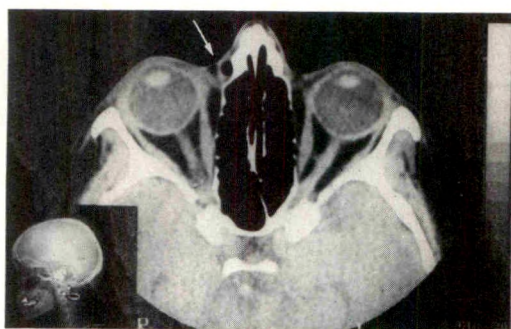
*Inquiries to Shmuel Levartovsky, M.D., Department of Ophthalmology, Kaplan Hospital, Rehovot 76100, Israel.*

Nasolacrimal duct obstruction is usually characterized by epiphora and recurrent episodes of dacryocystitis. Pain is restricted to episodes of dacryocystitis and generally confined to the inflamed sac.

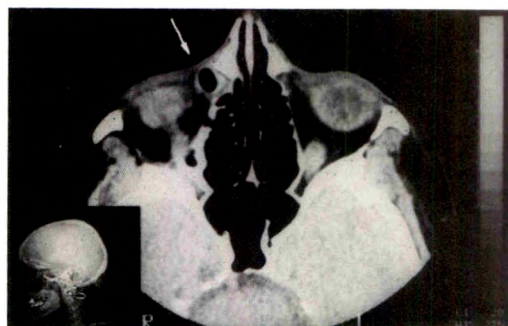
We examined a 42-year-old woman who had a ten-year history of frequent and recurrent episodes of severe right hemifacial pain. With each episode the patient noted the appearance of a cystic mass located medially and below the right medial canthus. Pressure on the mass provoked a white mucoid discharge from her right nostril. The patient denied any episodes of epiphora. The cystic mass was not present in the intervals between these attacks.

Her right upper hemifacial pain was so intense that she had dental extraction on that side, without alleviation of the symptoms. Subsequently, ethanol was injected into the right trigeminal ganglion, with no improvement.

On examination, a 7- to 10-mm cystic mass



**Fig. 1** (Levartovsky and Sade). Computed tomography disclosed a medial cystic mass that contains fluid as well as air (arrow).



**Fig. 2** (Levartovsky and Sade). Dilated nasolacrimal duct (arrow) in the same patient.

with a sensation of air crepitation was palpated over the right nasal bone extending toward the right medial canthus. Pressure on the mass produced a thick mucoid discharge from the right nostril. Computed tomography disclosed a right medial cystic mass (Fig. 1) containing fluid as well as air (white arrow). Lower sections (Fig. 2) demonstrated a dilated nasolacrimal duct (white arrow).

During the operation the region was exposed by a Lynch incision. A cystic inflamed lacrimal sac was found. The medial bony wall of the orbit adjacent to the slightly enlarged sac was found to be eroded into the nasal cavity across the lacrimal plate. The cystic sac was resected and a dacryocystorhinostomy was performed. Pathologic examination showed a thickened lacrimal sac wall with chronic inflammatory cell infiltration. One year after surgery, the patient is free of symptoms.

Congenital nasolacrimal duct mucocele has been described as causing nasal airway obstruction. In those cases the imperforate distal membrane of the nasolacrimal duct ballooned out, resulting in a submucosal cyst within the nasal cavity.<sup>1</sup> In our patient the enlarged lacrimal sac caused destruction of the bony wall over the sac. Air from the nasal cavity entered into that region, probably through the bony defect.

This case demonstrated that severe hemifacial pain caused by bony destruction may be a manifestation of a distended lacrimal sac.

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## Stiles-Crawford Effect and Color Matching in Stargardt's Disease

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Vivianne C. Smith, Ph.D.,  
Joel Pokorny, Ph.D.,  
and Marilyn B. Mets, M.D.

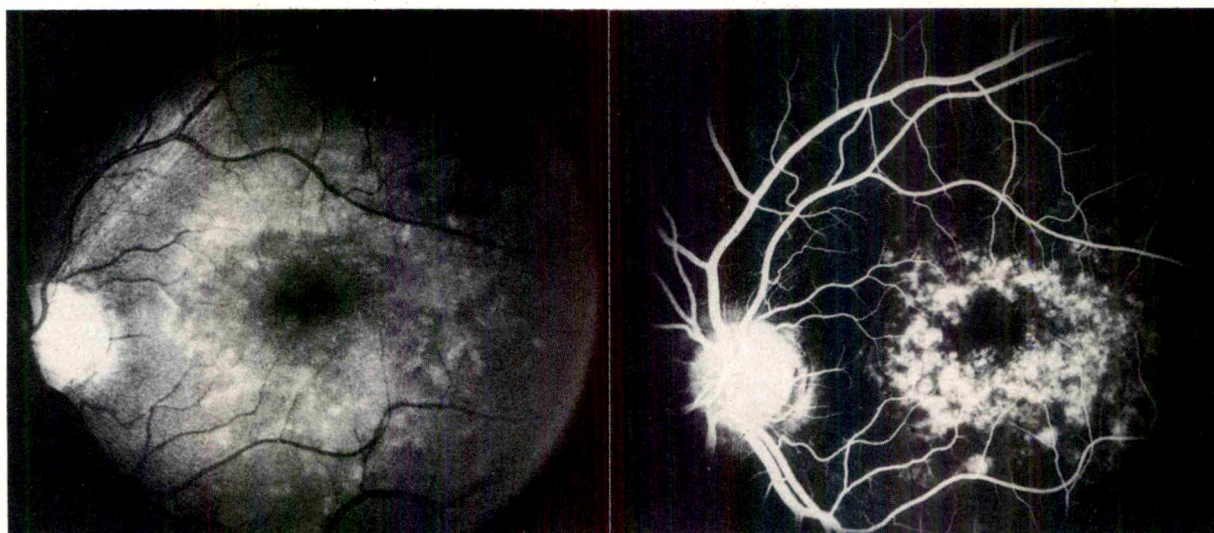
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We measured the Stiles-Crawford effect and performed color matching on a patient with Stargardt's disease (fundus flavimaculatus). Both psychophysical techniques demonstrated gross abnormalities at the level of the foveal photoreceptors in a fairly early stage of the disease. These data confirm the results of a study on foveal densitometry in Stargardt's disease,<sup>1</sup> in which impaired foveal cone photopigment kinetics were found at an early stage.

A 20-year-old woman noted a decrease in vision in her right eye over a one-week period. She was healthy, used no drugs, and her family history was noncontributory. At examination her corrected visual acuity was R.E.: 20/200 and L.E.: 20/30 +3. Slit-lamp examination of the lens showed the bilateral presence of three tiny, white dots just anterior and temporal to the anterior Y suture. Direct and indirect ophthalmoscopy showed clear media (the lens anomalies were not visible), and the fundus was vermillion. Flavimaculatus lesions were

seen around the vascular arcade and nasal to the optic disk. The lesions extended in the horizontal meridian from the raphe to the posterior pole (Fig. 1). The foveal reflexes were present but the perimacular reflexes were absent. Fluorescein angiography disclosed concentric annular macular lesions in both eyes with preservation of the central area, partly visible flavimaculatus lesions, and absence of choroidal fluorescence (Fig. 2). Static perimetry disclosed a dense central scotoma in the right eye and no abnormalities in the left eye. The Amsler grid in the left eye showed no metamorphopsia. The patient failed (both eyes) to identify most Ishihara plates and the red-green plates of the Standard Pseudoisochromatic Plates, part 2. In the left eye the Farnsworth-Munsell 100-hue test showed an abnormal square root total error score of 15 with no significant axis. The Rayleigh matches showed a rod-dominated match (perhaps caused by eccentric fixation) in the right eye and pseudoprotanomaly in the left eye. The Moreland matches (blue-green equation) were wide in the right eye and normal in the left eye. Results of electroretinography (both the normal clinical protocol and specialized short wavelength sensitive cone testing<sup>2</sup>) and electro-oculography were within normal limits in both eyes. The Stiles-Crawford effect (brightness matches employing a technique similar to that published elsewhere<sup>3</sup>) showed a flat function in the vertical meridian in both eyes (Fig. 2), and an essentially flat function in the horizontal meridian although, because of the lens anomalies,



**Fig. 1** (Keunen, and associates). Red-free fundus photograph showing widespread flavimaculatus flecks (left) and corresponding fluorescein angiogram (right) of the patient's left eye. The fluorescein angiogram shows characteristic blocked choroidal fluorescence with bullseye transmission defects.

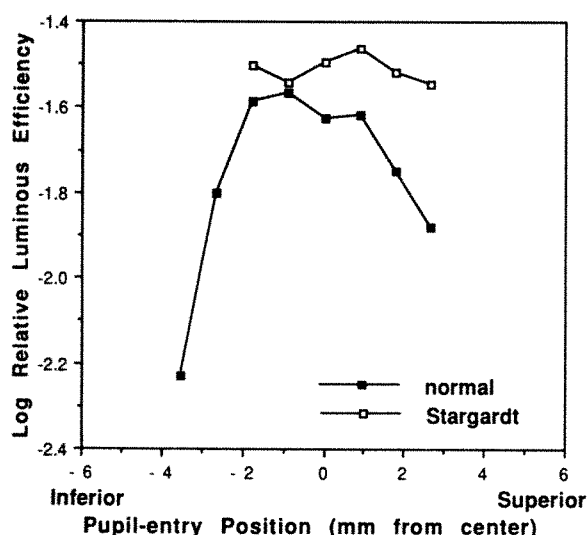


Fig. 2 (Keunen, and associates). The Stiles-Crawford effect in the vertical meridian of the left eye of a healthy subject (solid squares) is a parabolic function. The Stiles-Crawford effect in the patient with Stargardt's disease (open squares) shows essentially a flat function.

the function at the temporal side of the cornea was capricious. The data did not show the normal parabolic shape peaking near the zero entry position.

By psychophysical tests we confirmed a serious impairment of the foveal cone photoreceptors. The flat Stiles-Crawford data are consistent with a severe distortion of foveal cone photoreceptors, causing a decreased optical density of cones, which was documented by the pseudoprotonomaly on color matching.<sup>3</sup> An abnormal Stiles-Crawford measurement was reported in another patient with Stargardt's disease (fundus flavimaculatus),<sup>4</sup> but in this patient there were also cystoid macular changes. The damage to the foveal cones is remarkable in the left eye of our patient with a visual acuity of 20/30 +3, normal foveal appearance, no metamorphopsia, and unimpaired static perimetry. Also, the results of the electroretinography and electro-oculography were normal. Moloney, Mooney, and O'Connor<sup>5</sup> emphasized that electrodiagnosis is not particularly helpful in detecting photoreceptor damage in Stargardt's disease. These investigators also reported a rapid initial loss of visual acuity in three patients with Stargardt's disease.

A report on foveal densitometry<sup>1</sup> (a physiological method for noninvasive assessment of cone photoreceptors kinetics in vivo) disclosed poor foveal cone performance at early stages of Stargardt's disease. Those results are consis-

tent with the psychophysical data described in our patient. The pathogenesis of Stargardt's disease seems to start primarily at the level of the retinal pigment epithelium with an accumulation of acid mucopolysaccharide.<sup>6</sup> However, the Stiles-Crawford effect, color matching, and foveal densitometry indicate that the foveal photoreceptors may be affected during the early stage of the disease process, even when visual acuity is only mildly subnormal. Therefore, these specialized techniques may have clinical value for diagnosis in Stargardt's disease.

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## Chemosis Associated With Whipple's Disease

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A 59-year-old woman was examined in May 1990 for prolonged fever and acute chemosis of



the right eye. Eight months earlier, malabsorption syndrome had been diagnosed in another hospital. At that time the patient had had diarrhea of four weeks' duration, 10-kg body weight loss, moderate fever, and vomiting. Clinical examination showed melanoderma. Duodenal biopsies disclosed blunting of the villi with flattening of the mucosal epithelium and presence of foamy macrophages containing large cytoplasmic periodic acid-Schiff stain-positive granules. Laboratory studies disclosed a low serum albumin level (24.6 g/l), a low calcium concentration (77 mg/l), a microcytic anemia (hemoglobin, 10.3 mg/dl), and a normal erythrocyte sedimentation rate. The diagnosis of Whipple's disease was made in September 1989, and a regimen of oral doxycycline (300 mg per day) was initiated. Digestive symptoms disappeared, but fever persisted. A general practitioner gave her prednisone (30 mg per day) for six months with progressive reduction to 10 mg per day.

In January 1990, the initial ophthalmic examination disclosed bilateral cataract with visual acuity of R.E.: 1/20 and L.E.: 2/20. In April 1990, 15 days after corticosteroid withdrawal, fever reoccurred despite doxycycline therapy. At that time, conjunctival edema occurred rapidly with moderate proptosis of the right eye without ophthalmoplegia. Ocular examination showed conjunctival hyperemia and considerable chemosis in the right eye (Fig. 1). No keratitis was noted. Visual acuity was unchanged, and the fundus of the left eye was normal. The fundus of the right eye could not be seen because of the cataract. An orbital computed tomographic scan showed a thickened right lateral rectus muscle, which indicated ocular myositis (Fig. 2). Laboratory findings

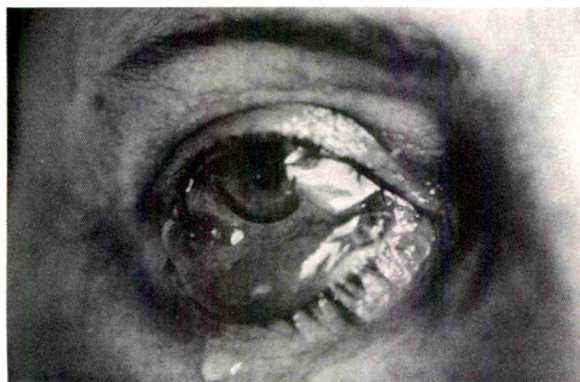


Fig. 1 (Disdier and associates). Chemosis of the right eye.

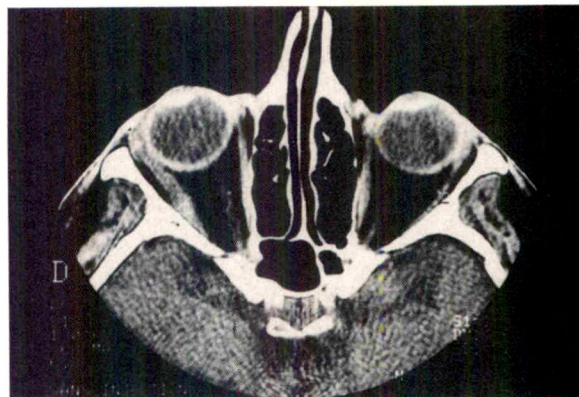


Fig. 2 (Disdier and associates). Computed tomographic scan of the orbits showing thickened right lateral rectus muscle.

disclosed an accelerated erythrocyte sedimentation rate (90 mm/hr), increased serum fibrin level (6.7 g/l), and normal lumbar puncture. Temporal artery biopsy and brain magnetic resonance imaging showed no abnormality. A second duodenal biopsy demonstrated persistence of periodic acid-Schiff stain-positive macrophages in the digestive mucosa.

In June 1990, therapy with sodium benzyl penicillin G (2,000,000 U per day) and streptomycin sodium (1 g per day) was started, which resulted in rapid improvement of the ocular signs and symptoms and disappearance of fever. From July to August 1990, the patient took sulfamethoxazole (1.6 g per day) and trimethoprim (320 mg per day). Since September 1990, a regimen of doxycycline (200 mg per day) and sulfamethoxazole-trimethoprim as rotated every four weeks without recurrence of chemosis, and erythrocyte sedimentation rate levels have been low (4 mm/hr).

Whipple's intestinal lipodystrophy is a rare disorder, and ocular involvement is an unusual manifestation. Previous reports described miscellaneous findings such as bilateral central scotoma, papilledema, vitreous opacities and hemorrhages, external ophthalmoplegia and keratitis, optic atrophy, gaze palsies, and nystagmus.<sup>1,2</sup> A slight chemosis associated with uveitis, glaucoma, epiphora, keratitis, and fibrovascular pannus involving the anterior chamber angles and corneal periphery was reported in one case.<sup>2</sup> In another patient who had ophthalmoplegia externa, asteroid hyalitis, and dementia, ultrastructural analysis of the rectus muscle biopsy specimen showed enlargement of mitochondria and presence of intracytoplasmic multilamellar bodies in muscle cells.<sup>1</sup> Our

patient had a clinical relapse of Whipple's disease with considerable chemosis and an ocular muscle involvement responsible for moderate proptosis. Corticosteroid therapy (which is not an accepted treatment of Whipple's disease<sup>3</sup>) and use of cycline alone, which has been reported with a 43% relapse rate,<sup>4</sup> probably played a role in the occurrence of the ocular lesions.

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### Correspondence

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Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

### A Physical Analysis of the Factors That Determine the Contour of the Iris

EDITOR:

In the article, "A physical analysis of the factors that determine the contour of the iris" by J. S. Tiedeman (*Am. J. Ophthalmol.* 111:338, March 1991), the author should be commended for presenting a cogent mathematical and physical analysis of iris contour.

As with any mathematical model, the validity of the analysis depends upon the validity of its fundamental assumptions. Presumably, Dr. Tiedeman chose equation (2) because it well

described the shape of the iris contour. Because of the computer iteration, it appears that the variable  $n$  is not restricted to the positive integers (as in the binomial theorem), but may be any real number. Nevertheless, polynomials in the form of equation (2) describe parabolas, cubics, quartics, and other such curves. One characteristic of such curves is that the radius of curvature is continuously variable from region to region. If the graphs in Figures 3 and 4 are accurate, it appears to me that the radius of curvature of the iris contour decreases as the root of the iris is approached.

I ask Dr. Tiedeman to consider an alternative approach to the initial assumption of equation (2). This approach involves the relationship between pressure  $P$ , surface tension  $\sigma$ , and radius of curvature  $R$ . The relationship applies to soap bubbles, balloons, Molteno blebs, and presumably iris contour. Pressure  $P$  is proportional to the ratio  $\sigma/R$ . A convenient example is a long balloon with a nipple at the end. We know that the pressure  $P$  is uniform at all points within the balloon. At the nipple, the surface tension  $\sigma$  and radius of curvature  $R$  are less than at the more inflated points on the balloon. Both  $\sigma$  and  $R$  are reduced proportionately as  $P$  remains constant.

Of course, surface tension  $\sigma$  is not the same as Tiedeman's scalar tension  $t$  in a cross section of iris unit segment. Surface tension  $\sigma$  is measured in work per unit area or force per unit width. Nevertheless, the two are closely related.

Now, if the pressure difference  $P$  between the posterior and anterior chambers and surface tension  $\sigma$  are uniform at all points along the iris contour, then we should expect a uniform radius of curvature  $R$  of the iris. This is true for soap bubbles and water droplets. Each cross section of iris unit segment would describe the arc of a circle. (The entire iris as a whole would not necessarily describe a sphere except in the special case where the extension of the arc intersected the opposite pupil margin and iris root.) In this case, equation (2) would be approximated by a function of the form,

$$R^2 = (r - h)^2 + (y - k)^2,$$

where  $y$  is the anterior displacement from the iris root plane of a point along the iris contour,  $r$  is the radial distance of that point from the center of the pupil, and  $h$  and  $k$  are the coordinates of the center of the circle describe by the iris arc.

If the observed cross-sectional iris contour



deviates from this predicted circular contour, and it seems to be based upon the excellent measurements of Anderson, Jin, and Wright,<sup>1</sup> then one of two conditions must exist. In the first instance, if the pressure difference  $P$  is uniform along the entire iris contour, then surface tension  $\sigma$  must decrease where radius of curvature  $R$  decreases peripherally. This might be plausible if we speculate that the scalar tension  $t$  is constant and associated with individual dilator muscle fibers. As these fibers diverge toward the iris periphery, the force per unit width (or surface tension  $\sigma$ ) must decrease. In the second instance, if we assume that surface tension  $\sigma$  is uniform at all points on the iris surface, then pressure  $P$  is greater at the periphery where radius of curvature  $R$  is lesser. This is also plausible if we allow that there could be a pressure gradient due to resistance to aqueous flow through a long narrow passage between the lens and iris. Anderson, Jin, and Wright<sup>1</sup> considered this possibility, but thought that it must not be acting because their observed contours varied little from Tiedeman's theoretical shape. However, it appears to me that both are true: that Tiedeman's model predicts well the shape of the observed iris contour and that surface tension differences, pressure gradient, or both, provide a physiologic explanation for the departure from an expected circular contour.

JEFFREY W. KALENAK, M.D.  
Cleveland, Ohio

#### Reply

##### EDITOR:

Dr. Kalenak has called attention to my equation (2), and proposes an alternative approach to it. As the text of my article states, equation (2) is used only for the purpose of calculating the radially projected area of a unit segment of iris. The calculation of the angle  $\Theta$ , from which the iris contour is determined through iterative steps, is not strongly dependent upon the curvature described by equation (2), and this point is discussed later in the article. The graphs in Figures 3 and 4 are not derived directly from equation (2), but they are derived from the iterative solution of  $\Theta$ , in the manner described in the paragraph following equation (9): "... once the angle  $\Theta$  is found, a small change in radial position,  $\sigma$ , can be multiplied

times the tangent of the angle  $\Theta$  to obtain a new set of starting coordinates. The new angle  $\Theta$  in this position can be found and the entire cross section can be calculated in stepwise fashion with a high precision if  $\sigma$  is kept suitably small." Indeed, these figures are accurate representations of the mathematically derived curves and were plotted with a computer graphics routine, using the program given in Figure 7.

Dr. Kalenak proposes that the concept of surface tension might be applied to the iris. He is correct in that the concept of surface tension is mathematically valid when applied to soap bubbles, balloons, and Molteno blebs, but these thin layers of material differ significantly from iris tissue. Soap bubbles and balloons are homogeneous and resist stretching equally in any direction. The iris clearly has a different resistance to stretch along its muscular elements (dilator muscle fibers) than it does to stretch in the perpendicular direction (across iris stroma). This inhomogeneity invalidates the use of the simple concept of surface tension to describe the complex forces acting within the iris. One of the assumptions made for the model, as stated in the text, is that "... there is no interaction between adjacent dilator fibers." The error introduced by this assumption is then discussed in the second paragraph of the Discussion section: "... This error [caused by neglecting the stromal elasticity] would be most significant at those places with the smallest predicted radius of curvature of the surface ..." This is exactly as Anderson, Jin, and Wright<sup>1</sup> found.

In presenting his example of a long balloon with a nipple at the end, Dr. Kalenak asserts that  $\sigma$  and  $R$  are proportional as  $P$  remains constant. This is true only in those areas where  $\sigma$  is constant, but most definitely not in the area of transition between low surface tension (the nipple) and high surface tension (the body of the balloon) where the curvature actually reverses locally surrounding the nipple, going through a region of infinite radius of curvature (but not infinite surface tension).

The significance of my model is that it is able to predict the actual contour of the iris in vivo. To the extent that the assumptions are valid, the model is valid. While a pressure gradient may exist to account for some measured differences from the predicted contour, Anderson, Jin, and Wright<sup>1</sup> have shown that the predictions are correct to a high degree of preci-

sion, and thus confirm the fundamental validity of the model.

J. S. TIEDEMAN, M.D.  
Durham, North Carolina

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### Reference

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### Delayed-Onset Pseudophakic Endophthalmitis

EDITOR:

In the article, "Delayed-onset pseudophakic endophthalmitis" by A. M. Fox, B. C. Joondeph, H. W. Flynn, Jr., S. C. Pflugfelder, and T. J. Roussel (*Am. J. Ophthalmol.* 111:163, February 1991), we congratulate the authors on their superb clinical study. Other investigators have called this entity "chronic bacterial endophthalmitis," as the authors point out. On the basis of our primate studies (1983-1985), we coined the term "anterior endophthalmitis," since the posterior capsule plays an important role in sequestering infectious organisms in the anterior segment.<sup>1-3</sup> Our primate studies accurately predicted the potential for this clinical syndrome in the setting of an extracapsular cataract extraction before the original clinical reports in 1986.<sup>4,5</sup>

Finally, we wish to point out that this primate model could be used to explore the vari-

ous therapeutic modalities reported by Fox and others in the controlled manner. This might help us to determine decisively the appropriate role of intracameral antibiotics (anterior chamber as well as intravitreal), implant removal, and oral antibiotics. The many questions raised concerning a fortunately rare clinical syndrome point to the use of a primate model to study these issues.

FRANCIS E. O'DONNELL, JR., M.D.  
TODD L. BEYER, D.O.  
St. Louis, Missouri

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**"AMA DE" Drug Evaluations, Subscription, 1991.** Published by the American Medical Association, 515 North State Street, Chicago, Illinois. Three loose-leaf binders in a slipcase. Updated quarterly with new pages and a newsletter, \$116 to AMA members, \$145 to nonmembers. Also available in a single annual volume (no updates) for \$75 to members and \$95 to nonmembers.

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**"PDR" Physician's Desk Reference, 1991, ed. 45.** Published by Medical Economics Company, Inc., Oradell, New Jersey. A single annual volume, 2,496 pages. Sent free to physicians; additional copies available for \$49.95. The same group also publishes the following: PDR for Ophthalmology, \$37.95; Drug Interactions and Side Effects Index, \$34.95; Indications Index, \$19.95; and others. The full text of all PDR publications is available on a CD-ROM (MS-DOS) for \$595. All the dosage, contraindications, and warning information in the PDR is available (verbatim) in a palm-size computer for \$249.

Reviewed by H. Stanley Thompson  
*Iowa City, Iowa*

As every physician knows, there is drug information everywhere, and it keeps arriving in

overwhelming quantities. The PDR is still a single volume but it seems to get bigger every year. Because it is published "with the cooperation of the manufacturers whose products appear in it, the PDR stays even-handed by reproducing, word for word, the product descriptions prepared, edited, and approved by the manufacturer for the official package inserts, and then providing the reader with various search strategies.

The AMA DE is now in a sturdy loose-leaf format, and it is arranged by disease categories into 88 chapters: the cardiovascular drugs are in one section and the ophthalmologic drugs in another section. The various drugs available to treat a given condition are covered in the same chapter and can be readily compared.

The USP DI is the biggest of the three. Volume I is an encyclopedic compendium of prescription drugs arranged alphabetically by generic name. The 25 pages of color illustrations of pills and capsules are arranged alphabetically, so that, for example, five different sets of amitriptyline tablets in various sizes can be seen side by side. This format has its pros and cons: if you have an orange pill in your hand, and all you know about it is that it says "MSD 697" on the side of the pill, it is hard to find out what the pill is until you look up MSD 697 in a nearby table and find that it is Dolobid 500 mg. But there is no Dolobid in the illustration pages, so you don't get visual confirmation until you look up Dolobid in another section and find that it is Diflunisal. A four-color illustration of Diflunisal is available. However, if you are holding a purple tablet with "GG" or "RUGBY" on it, the USP DI illustrations will eventually show that it is amitriptyline, 75 mg, generic, but the PDR will leave you completely at sea.

Taken together, the PDR, USP DI, and the AMA DE weigh 42 pounds. This is bad for the trees, bad for the landfills, and very inefficient. I hope that in a few years, following the lead of the PDR publications, we will be able to switch over completely to a machine-readable database. It might then be possible, by responding to various prompts, for a physician to ask the database some specific questions, such as: "What drug should I use to treat hypertension in a 42-year-old patient who is in the third

trimester of pregnancy and has congestive heart failure?" Until then, every physician must have access to drug information, and these three organizations are offering us access, each from a slightly different point of view.

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## The Book List

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**Clinical Procedures in Optometry.** By J. Boyd Eskridge, John F. Amos, and Jimmy D. Bartlett. Philadelphia, J. B. Lippincott, 1991. 808 pages, index, illustrated. \$125

**Color Atlas of Ophthalmic Surgery: Cataracts.** By Richard P. Kratz and H. John Shamma. Philadelphia, J. B. Lippincott, 1991. 226 pages, index, illustrated. \$150

**Color Atlas/Text of Ophthalmic Parasitology.** By B. H. Kean, Tsieh Sun, and Robert M. Ellsworth. New York, Igaku-Shoin Medical Publishers, Inc., 1991. 233 pages, index, illustrated. \$110

**Light: Medicine of the Future.** By Jacob Liberman. Santa Fe, New Mexico, Bear and Company Publishing, 1991. 251 pages, index, illustrated. \$22.95

**Neurologic Clinics.** Edited by Lenore A. Breen. Philadelphia, W. B. Saunders, 1991. 247 pages, index, illustrated. \$79 (per year individual), \$94 (per year institution)

**Vascular Tumors and Malformations of the Ocular Fundus.** By J. J. De Laey and M. Hanssens. Netherlands, Kluwer Academic Publishers, 1990. 241 pages, index, illustrated. \$121

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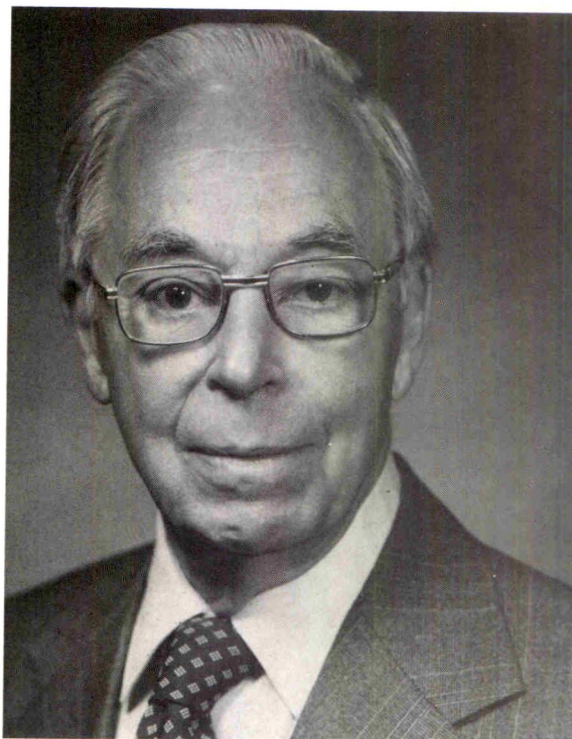
## Obituary

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### C. WILBUR RUCKER, M.D.

1900-1991

Charles Wilbur Rucker, B.S., M.D., M.S., in ophthalmology, consultant in ophthalmology at Mayo Clinic, Rochester, Minnesota from 1937 until 1967, head of the Department of Ophthalmology from 1949 until 1961, and professor of ophthalmology in the Mayo Graduate



C. Wilbur Rucker, M.D.

1990-1991

School of Medicine, died March 14, 1991, in Rochester, Minnesota.

Dr. Rucker was born Jan. 30, 1900, in Goodhue, Minnesota, the son of Elizabeth Olsen Rucker and Charles Edward Rucker. After high school in Red Wing, Minnesota, he attended the University of Minnesota, where he received his B.S. degree in 1922 and his M.D. degree in 1926, after completing a year of internship at Letterman General Hospital in San Francisco.

He entered the Mayo Foundation as a fellow in ophthalmology April 1, 1926, and spent 27 months in ophthalmology, three months in experimental surgery, and three months in otolaryngology and rhinology. He attended the University of Minnesota Medical School for six months. He was awarded the M.S. degree in ophthalmology in 1929. After leaving the Mayo Foundation July 1, 1929, he began a private practice in Minneapolis. He was appointed instructor in the University School of Medicine, as ophthalmologist in the Student Health Service, and was on the staff of Northwestern Hospital.

In 1937, Dr. Rucker rejoined the Mayo Clinic as consultant in ophthalmology and was ap-



pointed assistant professor of ophthalmology in the Mayo Graduate School of Medicine. He became associate professor in 1944 and professor in 1950. He was chairman of the Department of Ophthalmology from 1949 until 1961, and senior consultant until his retirement in 1967. He restricted his practice to medical ophthalmology and neuro-ophthalmology.

He was certified by the American Board of Ophthalmology in 1929, and in 1956 was elected to the Board. He served eight years as a director and four additional years as consultant, and as chairman in 1962 and 1963.

Dr. Rucker contributed over 100 published papers to the medical literature, most concerning medical ophthalmology, neuro-ophthalmology, and ophthalmic history. He collected old and rare ophthalmic books and donated these to the Mayo Medical Library. For many years he was an active member of the Mayo Medical Library Committee, and in 1972 the Library presented him with a plaque in recognition of his services.

He was a member of the American Medical Association (chair of the Section on Ophthal-

mology in 1962), the American Academy of Ophthalmology, the Minnesota Academy of Ophthalmology, the American Ophthalmological Society (74th president in 1970), the Alumni Association of the Mayo Graduate School of Medicine, the Phi Rho Sigma medical fraternity, the Society of Sigma Xi, and the Tau Kappa Epsilon academic fraternity.

Dr. Rucker was awarded the Lucien B. Howe medical twice: in 1966, from the Section on Ophthalmology and the American Medical Association, and in 1971 from the American Ophthalmological Society. In 1974, he received the Leslie Dana Medal from the Society for the Prevention of Blindness. He delivered the Gifford Memorial Lecture in Chicago in 1956, the Charles H. May Memorial Lecture in New York in 1960, and the de Schweinitz Lecture in Philadelphia in 1962. He was associate editor of the Archives of Ophthalmology.

He was married to Mabel (Mibs) Holaday of Webster City, Iowa, June 29, 1929. She died in 1990. Two sons, Dean A. and Charles E., both of Tucson, Arizona, survive.

ROBERT W. HOLLENHORST, SR.

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## ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

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**Survey of the optical quality of intraocular lens implants.** Grossman, L. W.\*, Igel, D. A., and Faaland, R. W.: *J. Cataract Refract. Surg.* 17:168, 1991.

### INTRAOCULAR LENSES, OPTICAL STANDARDS

Intraocular lenses from 15 United States firms were tested for conformance to the requirements of the American National Standards Institute Z80.7 standard for intraocular lenses. A total of 162 intraocular lenses were tested for resolution, astigmatism, and accuracy of labeled power. Average resolving power was 78% of the diffraction limit, much better than the minimum requirement, which is typically equivalent to 30% of the diffraction limit. This suggests that the Z80.7 requirement could be markedly tightened with little effect on current production practices. Only one intraocular lens exhibited astigmatism in excess of 0.25 diopters. Differences between measured and labeled power in excess of 0.50 diopters were found in 22 lenses, indicating that accuracy of refractive power may be the most common optical problem of the lenses.—Michael A. Kass

\*Office of Science and Technology, Center for Devices and Radiological Health, Food and Drug Administration, 1901 Chapman Ave., Rockville, MD 20857.

**A double-masked evaluation of lignocaine-prilocaine cream (EMLA) used to alleviate the pain of retrobulbar injection.** Sunderraj, P., Kirby, J., Joyce, P. W., and Watson, A.\*: *Br. J. Ophthalmol.* 75:130, 1991.

### RETROBULBAR INJECTION, PAIN, ANESTHETIC CREAM

A randomized, placebo controlled, double-masked study was undertaken in 115 patients undergoing cataract surgery to assess the efficacy of the anesthetic cream EMLA (eutectic mixture of local anesthetic, lignocaine-prilocaine) in alleviating the pain of retrobulbar injection. Sixty three patients received the EMLA cream and 52 the placebo cream. The pain was assessed objectively by the anesthetist, who ob-

served the reaction of the patient on needle insertion, and subjectively by the patient. Significantly lower pain scores were recorded in patients treated with EMLA cream (anesthetist's observation:  $p < 0.01$ , patient's assessment:  $p < 0.006$ ). No patients experienced serious side effects in either treatment group.—Authors' abstract

\*Department of Ophthalmology, District General Hospital, Southport PR8 6NJ.

**A randomized clinical trial of scatter photocoagulation of proliferative sickle cell retinopathy.** Farber, M. D.\*, Jampol, L. M., Fox, P., Moriarty, B. J., Acheson, R. W., Rabb, M. F., and Serjeant, G. R.: *Arch. Ophthalmol.* 109:363, 1991.

### SICKLE CELL RETINOPATHY, SCATTER PHOTOCOAGULATION THERAPY

A randomized prospective clinical trial of argon laser scatter photocoagulation therapy for proliferative sickle cell retinopathy was performed on 116 patients (174 eyes) in Kingston, Jamaica. Ninety-nine eyes were treated with scatter photocoagulation and 75 eyes served as controls. The average length of follow-up was 42 months for the control eyes and 47 months for the treated eyes. Prolonged loss of visual acuity was statistically significantly reduced in the treated eyes. The incidence of vitreous hemorrhage was also significantly reduced in the treated eyes after controlling for the previously defined risk factors of vitreous hemorrhage and extent of proliferative sickle cell retinopathy at entry into the study. There were no complications associated with argon laser scatter photocoagulation. Scatter photocoagulation of proliferative sickle cell retinopathy is currently the most effective and safe way to treat patients with sea fan neovascularization.—Authors' abstract

\*Department of Ophthalmology, UIC Eye Center, University of Illinois at Chicago, 1855 W. Taylor St., Chicago, IL 60612.



**Blood contacts during surgical procedures.**

Panlilio, A. L. \*, Foy, D. R., Edwards, J. R., Bell, D. M., Welch, B. A., Parrish, C. M., Culver, D. H., Lowry, P. W., Jarvis, W. R., and Perlino, C. A.: JAMA 265:1533, 1991.

**SURGERY, BLOOD CONTACT, OPERATING ROOM PERSONNEL**

Operating room personnel are at risk for infection with blood-borne pathogens through blood contact. To describe the nature and frequency of blood contact and its risk factors, trained observers monitored a sample of operations performed by six surgical services at Grady Memorial Hospital, Atlanta, Ga., for 6 months. In 62 (30.1%) of 206 operations, at least one blood contact was observed. Of 1828 operating room person-procedures observed, 96 (5.2%) had 147 blood contacts (133 skin contacts [90%], 10 percutaneous injuries [7%], and four eye splashes [3%]). The mean number of blood contacts per 100 person-procedures was highest for surgeons (18.6). The frequency of percutaneous injury was similar among surgeons and scrub staff (mean, 1.2 per 100 worker-procedures for each group). Risk factors for surgeons' blood contacts were (1) performing a trauma, burn, or orthopedic emergency procedure (odds ratio [OR], 4.1; 95% confidence interval [CI], 2.0 to 8.7); (2) patient blood loss exceeding 250mL (OR, 2.1; 95% CI, 1.2 to 3.7); and (3) being in the operating room longer than 1 hour (OR, 3.3; 95% CI, 1.6 to 7.1). Of 100 blood contacts among surgeons, 81 (74%) were potentially preventable by additional barrier precautions, such as face shields and fluid-resistant gowns. Twenty-one (84%) of 25 blood contacts among surgeons in procedures in which all three risk factors were present were potentially preventable by additional barriers. Of 29 blood contacts among anesthesia and circulating personnel, 20 (69%) would have been prevented by glove use. For surgical procedures in which operating room personnel are at increased risk of blood contact, reevaluation of surgical technique, use of appropriate barrier precautions, and development of puncture-resistant glove materials are indicated.—Authors' abstract

\*Hospital Infections Program, Centers for Disease Control, Mailstop C-10, Atlanta, GA 30333.

**Clinical Use of Ultrasound Biomicroscopy.**

Pavlin, C. J. \*, Harasiewicz, K., Sherar, M. D.,

and Foster, F. S.: Ophthalmology 98:287, 1991.

**ULTRASOUND BIOMICROSCOPY, VISUALIZATION OF OCULAR STRUCTURES**

The authors have developed a method of obtaining images of cross-sections of the intact anterior globe at microscopic resolution. High-frequency ultrasound transducers (50–100 MHz) have been developed and incorporated into a clinical B-scan device capable of producing images in the living human eye to a depth of approximately 4 mm at an axial and lateral resolution approaching 20  $\mu$ m. Clinical use of this instrument is no more difficult than conventional immersion ultrasonography. The authors' results in a series of 14 clinical cases have shown that this method can provide information unavailable from any other imaging technique. Anterior segment tumors difficult to define with conventional ultrasound can be measured and the extent of invasion determined. Differentiation of tissue on the basis of internal acoustic characteristics is aided by the very fine backscatter speckle patterns at these frequencies. Pathology behind anterior segment opacities can be imaged in detail and the ability to image angle structures in cross-section allows a new quantitative method of gonioscopy. The ability to define the relationship of the iris, posterior chamber, zonules, ciliary body, and lens is potentially helpful in understanding mechanisms of glaucoma. Ocular structures can be measured with increased accuracy. Clinical ultrasound biomicroscopy (UBM) has shown significant potential as an aid in diagnoses of ocular disease.—Authors' abstract

\*Ocular Oncology Clinic, Princess Margaret Hospital, 500 Sherbourne St., Toronto, Ontario, Canada M4X 1K9.

**The incidence of ulcerative keratitis among aphakic contact lens wearers in New England.**

Glynn, R. J., Schein, O. D., Seddon, J. M. \*, Poggio, E. C., Goodfellow, J. R., Scardino, V. A., Shannon, M. J., and Kenyon, K. R.: Arch. Ophthalmol. 109:104, 1991.

**CONTACT LENS WEAR, ULCERATIVE KERATITIS**

We conducted a population-based incidence study in five New England states to quantify the risk of ulcerative keratitis associated with con-

tact lens use among aphakic persons. All practicing ophthalmologists in the five-state area were surveyed to identify prospectively all new cases of ulcerative keratitis during a 4-month period. The number of aphakic persons using specific types of contact lenses was estimated through a telephone survey of 4178 households identified by random digit dialing. The annualized incidence of ulcerative keratitis among aphakic persons using contact lenses was estimated to be 52 cases per 10,000 aphakic contact lens wearers (95% confidence interval (CI), 31.1 to 86.9). The risk of ulcerative keratitis varied substantially by lens use, with extended wear having an estimated seven-fold greater risk relative to daily wear (95% CI, 1.6 to 30.2). Rates of ulcerative keratitis in aphakic persons using contact lenses were much greater than rates among cosmetic wearers of the same lens type: for daily-wear lenses, aphakic persons were estimated to have 6.3 times the risk of cosmetic wearers (95% CI, 1.9 to 21.0), and for extended-wear lenses, aphakic persons were estimated to have 8.7 times the risk of cosmetic wearers (95% CI, 3.5 to 21.9). These risks are useful in assessing the benefits and risks of contact lens wear as an alternative to other methods of aphakic correction.—Authors' abstract

\*Epidemiology Unit, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

**Nyctalopia with normal rod function: A suppression of cones by rods.** Falcao-Reis, F. M., Hogg, C. R., Frumkes, T. E., and Arden, G. B.\*: *Eye* 5:138, 1991.

#### ROD CONE INTERACTION, NIGHT BLINDNESS

Twenty-nine patients with exaggerated rod-cone interaction are described. All were referred because they appeared to suffer from night blindness. ERG and EOGs were performed but were normal. However, investigation with a modified dark-adaptometry technique showed that in these patients cone flicker thresholds rise considerably more during dark adaptation than is normal, and this is sufficient to explain the symptoms. In one case, the condition appears familial. Many patients report their symptoms begin in early adult life and slowly get worse, but we have no objective evidence of progression.—Authors' abstract

\*Electrodiagnostic clinic, Moorfields Eye Hospital, City Rd., EC1V 2PD London, U.K.

**Recoverin: A calcium sensitive activator of retinal rod guanylate cyclase.** Dizhoor, A. M., Ray, S., Kumar, S., Niemi, G., Spencer, M., Brolley, D., Walsh, K. A., Philipov, P. P., Hurley, J. B.\*, and Stryer, L.: *Science* 251:915, 1991.

#### PHOTOEXCITATION, CYCLIC GMP, RECOVERIN

Vertebrate retinal photoreceptors recover from photoexcitation-induced hydrolysis of guanosine 3', 5'-monophosphate (cyclic GMP) by resynthesizing cyclic GMP, which reopens cation channels that have been closed by light. Activation of guanylate cyclase by light-induced depletion of cytosolic calcium is a key event in this recovery process. This cyclase has now been shown to be regulated by a 23-kilodalton calcium binding protein. The protein is present in both rod and cone photoreceptors and was named recoverin because it promotes recovery of the dark state. The amino acid sequence of recoverin exhibits three potential calcium binding sites (EF hands). That recoverin binds calcium was confirmed with calcium-45 and by observing calcium-induced changes in its tryptophan fluorescence. Recoverin activated guanylate cyclase when free calcium was lowered from 450 to 40 nM, an effect that was blocked by an antibody to recoverin. Thus, guanylate cyclase in retinal rods is stimulated during recovery by the calcium-free form of recoverin. A comparison of recoverin with other calcium binding proteins reveals that it may represent, along with the protein visinin, a family of proteins that are regulated by submicromolar calcium concentrations.—Authors' abstract

\*Department of Biochemistry and Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195.

**Hospital cost containment in the 1980s. Hard lessons learned and prospects for the 1990s.** Schwartz, W. B.\*, and Mendelson, D. N.: *N. Engl. J. Med.* 324:1037, 1991.

#### COST CONTAINMENT, NUMBER OF INPATIENT DAYS, NUMBER OF ADMISSIONS

A key strategy used to contain hospital costs during the 1980s was to reduce the total number of admissions and the average length of stay. Using data from the American Hospital Association and the Health Care Financing Ad-



ministration, the authors calculated the savings in the total number of inpatient days as the deviation from the historical increase in the number of inpatient days per year. They then estimated the increase in costs that would have been observed if the reduction in the number of inpatient days had not occurred. Finally, the authors compared the rates of increase in hospital reimbursement for Medicare beneficiaries and for patients not covered by Medicare.

The total number of inpatient days per year decreased by 28% between 1981 and 1988. The annual reduction was greatest in 1984 and 1985 and became progressively smaller in each subsequent year; by 1988, there was virtually no further reduction in the total number of inpatient days. The brief slowing of the increase in costs in the mid-1980s can be attributed entirely to the reduction in the number of inpatient days per year. The underlying rate of increase in costs was thus unaffected by efforts to contain spending.

An increased number of outpatient visits partially offset the savings that resulted from the reduction in the number of inpatient days. This increase persisted even when the savings that were the results of the lower number of inpatient days dwindled, and it virtually eliminated any dollar savings during the latter part of the 1980s. Between 1976 and 1982, Medicare spending on services provided by acute-care hospitals increased by 9.2% per year in real terms, whereas non-Medicare expenditures increased by only 4.6%. This pattern has been reversed in recent years; from 1987 through 1988, Medicare spending increased by only 0.6% per year, whereas non-Medicare spending increased by 9%. It thus appears that the era of easy reductions in the number of inpatient days, with the associated attenuation of increasing costs, is largely over. If further reductions in inpatient days are accompanied by an increase in the amount of ambulatory care similar to that seen during the past few years, the net savings will probably be negligible. Once the potential savings resulting from reductions in the number of inappropriate inpatient days has been exhausted, real hospital costs can be expected to increase, unless other effective measures to contain costs are implemented.—Michael A. Kass

\*Department of Medicine, Tufts University School of Medicine, 136 Harrison Ave., Boston, MA 02111.

**How well has Canada contained the costs of doctoring?** Hughes, J. S.\*: JAMA 265:2347, 1991.

#### CANADA, COST CONTAINMENT, NUMBER OF PHYSICIANS, INCREASED UTILIZATION

Canada's provinces have had varying success at containing the costs of physician services through the use of fee schedules and expenditure targets. This article examines the wide variation in the increases in the costs of physician services among Ontario, Quebec, and British Columbia between 1975 and 1987. Cost increases during that time resulted from various combinations of increases in prices (fees) and utilization, stimulated by an increased supply of physicians. Differences among the three provinces resulted from differences in the aggressiveness of fee schedule controls and whether expenditure targets were imposed. Regardless of the degree of expenditure increases, utilization increased steadily in all three provinces and was associated most consistently with growth in the supply of physicians. This was most dramatically illustrated in Quebec, which noted the most rapid rise in physician-to-population ratio. Cost containment may ultimately require constraints on the number of new physicians in addition to controls on fees and utilization.—Author's abstract

\*Dana Diagnostic Center, Yale-New Haven Hospital, New Haven, CT 06504.

**The origin of the full-time faculty system. Implications for clinical research.** Fye, W. B.\*: JAMA 265:1555, 1991.

#### FULL-TIME FACULTY, CLINICAL RESEARCH, PATIENT RELATED ACTIVITY

Clinical research has long been viewed as a fragile pursuit requiring special nurturing. The full-time clinical faculty system was introduced in the early 20th century to provide a milieu that would foster clinical investigation. This article, based on extensive archival research, will show that the main goal of the architects of the full-time system was to stimulate research by removing the incentive for medical professors to devote their main energy to practice. The plan was developed by preclinical scien-

tists at The Johns Hopkins Medical School (Baltimore, MD) and was inaugurated there in 1913 with the financial assistance of the Rockefeller General Education Board. As other medical schools adopted traditional academic criteria for appointment and advancement, there were additional incentives for faculty members to undertake research. In the 1920s, the General Education Board yielded to pressure to liberalize its definition of full time and began to support medical schools that implemented what came to be known as the "geographic full-time plan." Increased government support and other factors encouraged the expansion of full-time plans and led to an impressive increase in the output of research. Today, growing pressure on full-time clinical faculty members to generate income from practice for themselves and their institutions threatens the future of clinical research in this country.—Author's abstract

\*Cardiology Department, Marshfield Clinic, 1000 North Oak Ave., Marshfield, WI 54449-5777.

#### **Do house officers learn from their mistakes?**

Wu, A. W.\*, Folkman, S., McPhee, S. J., and Lo, B.: JAMA 265:2089, 1991.

#### **MEDICAL MISTAKES, ADVERSE OUTCOMES, LEARNING FROM THE MISTAKE**

Mistakes are inevitable in medicine. To learn how medical mistakes relate to subsequent changes in practice, we surveyed 254 internal medicine house officers. One hundred fourteen house officers (45%) completed an anonymous questionnaire describing their most significant mistake and their response to it. Mistakes included errors in diagnosis (33%), prescribing (29%), evaluation (21%), and communication (5%) and procedural complications (11%). Patients had serious adverse outcomes in 90% of the cases, including death in 31% of cases. Only 54% of house officers discussed the mistake with their attending physicians, and only 24% told the patients or families. House officers who accepted responsibility for the mistake and discussed it were more likely to report constructive changes in practice. Residents were less likely to make constructive changes if they attributed the mistake to job overload. They were more likely to report defensive changes if

they felt the institution was judgmental. Decreasing the work load and closer supervision may help prevent mistakes. To promote learning, faculty should encourage house officers to accept responsibility and to discuss their mistakes.—Authors' abstract

\*Johns Hopkins University, 624 N. Broadway, Baltimore, MD 21205.

#### **A prospective study of advance directives for life-sustaining care.** Danis, M.\*, Southerland, L. I., Garrett, J. M., Smith, J. L., Hielema, F., Pickard, C. G., Egner, D. M., and Patrick, D. L.: N. Engl. J. Med. 324:882, 1991.

#### **ADVANCE DIRECTIVES, TREATMENT PREFERENCES, LIFE-SUSTAINING CARE**

The use of advance directives is recommended so that people can determine the medical care they will receive when they are no longer competent. In a prospective study conducted over a two-year period, 126 competent residents of a nursing home and 49 family members of incompetent patients were interviewed to determine their preferences with respect to hospitalization, intensive care, cardiopulmonary resuscitation, artificial ventilation, surgery and tube feeding in the event of critical illness, terminal illness or permanent unconsciousness. Advance directives, consisting of signed statements of treatment preferences, were placed in the medical record to assist in care in the nursing home and to be forwarded to the hospital if necessary. During 96 hospitalizations or deaths in the nursing home, care was consistent with previously expressed wishes 75% of the time. Among the 24 cases in which inconsistencies occurred, six involved care that was provided more aggressively than had been requested, and 18 involved care that was less aggressive than had been requested. Inconsistencies were more likely in the nursing home than in the hospital.—Michael A. Kass

\*Division of General Medicine and Clinical Epidemiology, Campus Box 7110, 5025A Old Clinic Bldg., University of North Carolina, Chapel Hill, NC 27599-7110.

#### **Visuospatial impairment in Parkinson's disease.** Levin, B. E., Llabre, M. M., Reisman, S.,



Weiner, W. J., Sanchez-Ramos, J., Singer, C., and Brown, M. C.: *Neurology* 41:365, 1991.

#### **PARKINSON'S DISEASE, VISUOSPATIAL DEFICITS, DEMENTIA**

There have been a number of reports of visual deficits in patients with Parkinson's disease. However, little is known about the rate of progression of these deficits and whether visuospatial functions are selectively involved or part of global dementia. A cohort of 183 patients with idiopathic Parkinson's disease and 90 control subjects underwent six different tests of visuospatial functioning. The patients were classified as to whether they had early (one to four years), middle (five to ten years), or advanced (ten or more years) disease. Performance deteriorated in five of the six visuospatial measures as a function of disease duration. The results were not influenced by age or anticholinergic medication. Facial recognition was the first visuospatial skill to deteriorate in Parkinson's disease. These findings suggest that visuospatial deficits are common in patients with Parkinson's disease. Whereas some of the deficits are related to dementia, others are independent of dementia.—Michael A. Kass

\*Department of Neurology (D4-5), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.

**Congenital-type nystagmus emerging in later life.** Gresty, M. A.\*, Bronstein, A. M., Page, N. G., and Rudge, P.: *Neurology* 41:653, 1991.

#### **LATE-ONSET NYSTAGMUS**

Six patients developed floricid nystagmus with consequent visual symptoms as teenagers or adults. In three patients, previous ophthalmic examination had failed to detect nystagmus. Results of ophthalmic and neurologic examinations were unremarkable and no neurologic diseases have developed in these patients over a follow-up of two to 15 years. Ocular movement recordings showed the nystagmus to be indistinguishable from congenital nystagmus, which usually becomes manifest in early infancy. It appears that a congenital-type nystagmus can emerge spontaneously in later life and that

the nystagmus does not imply a developing neurologic disorder.—Michael A. Kass

\*Medical Research Council, Human Movement and Balance Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, U.K.

**Early botulinum toxin treatment of acute sixth nerve palsy.** Murray, A. D. N.\*: *Eye* 5:45, 1991.

#### **SIXTH NERVE PALSY, BOTULINUM TREATMENT MEDIAL RECTUS MUSCLE**

Eight patients with total sixth nerve palsy were treated with botulinum toxin injection to the antagonist non-paretic medial rectus, within eight weeks of the onset of the palsy. Within a few days seven of the eight gained fusion without the necessity of a marked head turn, and none complained of confusing reversal of diplopia. The same seven recovered full function. The mean follow-up period after the last injection was 20 months.

Seven palsies were the result of head trauma and one was due to cerebro-vascular disease.

This preliminary report suggests that early botulinum toxin injection of patients with recent onset sixth nerve palsy is beneficial. Although all of the patients may possibly have recovered full lateral rectus function without treatment, the aetiologies of their palsies were of the type that frequently do not resolve. A randomized double-blind study is necessary more precisely to determine the effectiveness of this form of therapy.—Author's abstract

\*Department of Ophthalmology, University of Cape Town Medical School, Observatory, 7925, South Africa.

**Serum lipids and lipoproteins are less powerful predictors of extracranial carotid artery atherosclerosis than are cigarette smoking and hypertension.** Homer, D., Ingall, T. J., Baker, Jr., H. L., O'Fallon, W. M., Kottke, B. A., and Whisnant, J. P.\*: *Mayo Clin. Proc.* 66:259, 1991.

#### **CAROTID ARTERY ATHEROSCLEROSIS, SMOKING, HYPERTENSION, LOW-DENSITY LIPOPROTEIN CHOLESTEROL**

The effect of serum lipids and lipoproteins on extracranial carotid artery atherosclerosis was studied in patients who underwent carotid arteriography. Serum lipid and lipoprotein values along with data on other potential predictors of extracranial carotid artery atherosclerosis were determined in 240 patients who had at least one extracranial carotid artery visualized. In a multiple logistic regression analysis, the independently significant predictors of extracranial carotid artery atherosclerosis were, in decreasing order of significance, duration of smoking of cigarettes, hypertension, age, and low-density lipoprotein cholesterol. Serum cholesterol, triglycerides, high-density lipoprotein cholesterol, and apolipoprotein A-I did not show an independent effect. Although low-density lipoprotein cholesterol was an independent predictor of extracranial carotid artery atherosclerosis, its effect as a predictor was far outweighed by the effects of the duration of smoking of cigarettes and a history of hypertension.—Michael A. Kass

\*Department of Health Sciences Research, Mayo Clinic, Rochester, MN 55905.

**Frequency and clinical significance of Lyme seropositivity in patients with isolated optic neuritis.** Jacobson, D. M.\*, Marx, J. J., and Dlesk, A.: *Neurology* 41:706, 1991.

#### OPTIC NEURITIS, LYME DISEASE

Antibody reactivity against *Borrelia burgdorferi* was examined in 20 consecutive patients with newly diagnosed isolated optic neuritis who resided in a region endemic for Lyme disease. Four of 20 (20%) patients had positive results of serum biochemical analysis. All three patients who had follow-up serum biochemical analyses performed showed increasing convalescent concentrations of *Borrelia*-specific IgM. One patient refused lumbar puncture, one had clinically normal cerebrospinal fluid constituents except for an increased Lyme-antibody index, and two had cerebrospinal fluid lymphocytic pleocytosis that remained unexplained after extensive evaluations for causes other than Lyme disease. We treated both patients who had pleocytosis with intravenously administered ceftriaxone; the pleocytosis and optic nerve function improved. In the other two pa-

tients orally administered antibiotics contributed to excellent recovery of visual acuity. Serologic testing for Lyme disease may be warranted for human beings with optic neuritis who reside in an endemic region. Patients with increasing convalescent antibody concentrations or unexplained cerebrospinal pleocytosis should receive antibiotic treatment for Lyme disease.—Michael A. Kass

\*Neuro-ophthalmology (4F), Marshfield Clinic, 1000 North Oak Ave., Marshfield, WI 54449.

**Retinal ganglion cell loss is size dependent in experimental glaucoma.** Glovinsky, Y., Quigley, H. A.\*, and Dunkelberger, G. R.: *Invest. Ophthalmol. Vis. Sci.* 32:484, 1991.

#### EXPERIMENTAL GLAUCOMA, PREFERENTIAL LARGE GANGLION CELL LOSS

Thirty-two areas located in the temporal mid-peripheral retina were evaluated in whole-mount preparations from four monkeys with monocular experimental glaucoma. Diameter frequency distributions of remaining ganglion cells in the glaucomatous eye were compared with corresponding areas in the normal fellow eye. Large cells were significantly more vulnerable at each stage of cell damage as determined by linear-regression analysis. The magnitude of size-dependent loss was moderate at an early stage (20% loss), peaked at 50% total cell loss, and decreased in advanced damage (70% loss). In glaucomatous eyes, the lower retina had significantly more large cell loss than the corresponding areas of the upper retina. In optic nerve zones that matched the retinal areas studied, large axons selectively were damaged first. Psychophysical testing aimed at functions subserved by larger ganglion cells is recommended for detection and follow-up of early glaucoma; however, assessment of functions unique to small cells is more appropriate for detecting change in advanced glaucoma.—Authors' abstract

\*Maumenee B110, Wilmer, Johns Hopkins Hospital, 600 N. Wolfe, Baltimore, MD 21205.

**Effects of apomorphine, a dopamine receptor agonist, on ocular refraction and axial elon-**



**gation in a primate model of myopia.** Iuvone, P. M.\*, Tigges, M., Stone, R. A., Lambert, S., and Laties, A. M.: *Invest. Ophthalmol. Vis. Sci.* 32:1674, 1991.

#### MYOPIA, ANIMAL MODEL, DOPAMINE AGONIST

The authors examined the effect of local administration of a dopamine receptor agonist on visual deprivation-induced excessive ocular growth and myopia. Eight rhesus monkeys were monocularly deprived of vision from birth with opaque contact lenses. Four of the monkeys received drops of 1% apomorphine HCL 2-3 times/day in the occluded eye; the four control monkeys received vehicle only. Axial lengths were determined by A-scan ultrasonography at birth and at 5-7 months of age. The authors assessed the axial elongation by comparing the postnatal growth in the axial dimension of the occluded eyes with the postnatal growth in nonoccluded eyes. In three of the four control

monkeys, occlusion increased axial growth by an average of 1.3 mm. In contrast, they found that growth of the occluded and nonoccluded eyes of the apomorphine-treated monkeys was equivalent, except in one monkey whose non-occluded eye did not develop normally and was anomalously small. At 6.5-9.5 months of age, three of four controls had myopic refractive errors (-3 to -7 diopters) in the occluded eyes; three or four of the apomorphine-treated monkeys had hyperopic refractive errors (+1 - +3 diopters) in their occluded eyes. The occluded eye of the fourth monkey was only -0.5 diopters myopic. The findings suggest that apomorphine administration retards excessive axial elongation and the concomitant development of myopia associated with visual deprivation in primates.—Authors' abstract

\*Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322.

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## NEWS ITEMS

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**Send News Items to**  
**American Journal of Ophthalmology**  
**435 N. Michigan Ave., Suite 1415**  
**Chicago, IL 60611**

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

### **IX Congress of the European Society of Ophthalmology**

The IX Congress of the European Society of Ophthalmology and the first joint meeting with the European Academy of Ophthalmology will be held May 24–28, 1992, in Brussels, Belgium. For additional information, write Congress Ophthalmology 1992, Brussels International Trade Fair, Belgplein, B-1020 Brussels, Belgium.

### **International Society for Optical Engineering: Ophthalmic Technologies II**

The International Society for Optical Engineering will hold Part 2 of Biomedical Optics '92, Jan. 19–24, 1992, in Los Angeles. For additional information, write Roberta Hart, SPIE, P.O. Box 10, Bellingham, WA 98227-0010; telephone (206) 676-3290.

### **Hyderabad Academy of Ophthalmology: 4th Global Intraocular Lens and Refractive Keratoplasty Workshop**

The Hyderabad Academy of Ophthalmology, Hyderabad, India, will hold its 4th Global Intraocular Lens and Refractive Keratoplasty Workshop Jan. 29 and 30, 1992, in New Delhi, India. For more information, write C. S. Reshmi, M.D., Reshmi Eye Care Center, 2639 Brownsville Rd., Pittsburgh, PA 15227; telephone (412) 881-4242.

### **Volunteer Eye-Surgeon's Association: 2nd International Meeting**

The Volunteer Eye-Surgeon's Association will hold its 2nd International Meeting Oct. 11 and 12, 1991, at Anaheim, California. For fur-

ther information, write Robert C. Welsh, M.D., 1600 Onaway Dr., Miami, FL 33133; telephone (305) 856-1375 (nights).

### **Bascom Palmer Eye Institute: Retina Update Course**

Bascom Palmer Eye Institute of the Miami School of Medicine will offer a Retina Update Course Dec. 6 and 7, 1991, in Miami, Florida. For more information, write Continuing Education in Ophthalmology, P.O. Box 015869, Miami, FL 33101; telephone (305) 326-6099.

### **Hôpital Sainte-Justine: 16th Annual Pediatric Ophthalmology Day**

The Hôpital Sainte-Justine of Montreal will hold the 16th Annual Pediatric Ophthalmology Day Nov. 1, 1991. For more information, write Jean Milot, M.D., Department of Ophthalmology, Hôpital Sainte-Justine, 3175, chemin Côte-Sainte-Catherine, Montreal (Quebec) H3T 1C5 Canada; fax (514) 345-4805.

### **Massachusetts Eye and Ear Infirmary: Extracranial Optic Nerve Decompression Meeting**

The Departments of Ophthalmology and Otolaryngology at the Massachusetts Eye and Ear Infirmary will sponsor the Extracranial Optic Nerve Decompression Meeting, Nov. 2 and 3, 1991, in Boston, Massachusetts. For more information, write Michael P. Joseph, M.D., Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114; telephone (617) 573-3192.

### **New York Medical Center: Basic Science Course in Ophthalmology**

The New York Medical Center and the Post-Graduate Medical School will offer a Basic Science Course in Ophthalmology, Sept. 3–Dec. 20, 1991, at Bellevue Hospital, New York City. For further information, write NYU Medical Center, Post-Graduate Medical School, 550 First Ave., New York, NY 10016; telephone (212) 263-5295.

### **University of North Carolina: Ophthalmology Residents' Day**

The Department of Ophthalmology at the University of North Carolina at Chapel Hill will hold Ophthalmology Residents' Day Dec. 7,



1991. For further information, write Ms. Christine C. Cotton, Department of Ophthalmology, CB #7040, 617 Burnett-Womacks Bldg., University of North Carolina, Chapel Hill, NC 27599-7040; telephone (919) 966-5296.

**Prentice Eye Institute and St. Luke's Medical Center: Frontiers in Ophthalmology**

The 18th Annual Frontiers in Ophthalmology seminar, sponsored by the Prentice Eye Institute and St. Luke's Medical Center, Phoenix, will be Feb. 20-22, 1992, at Red Lion's LaPosada Resort in Scottsdale, Arizona. For more information, write Campbell Meeting Management, 1419 E. Divot Dr., Tempe, AZ 85283; telephone (602) 820-7027.

**Scheie Eye Institute: 7th Annual Symposium on Low Vision**

The 7th Annual Symposium on Low Vision will be held at the Scheie Eye Institute in Philadelphia, Pennsylvania, Sept. 21, 1991. For additional information, write Charlotte Beurer,

Scheie Eye Institute, Department of Ophthalmology, 51 N. 39th St., Philadelphia, PA 19104; telephone (215) 662-8141.

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**Personals**

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**Robert Folberg**

Robert Folberg has been named to the Frederick C. Blodi Professorship in Ophthalmology at the University of Iowa. Dr. Folberg is professor of ophthalmology and pathology, and director of the Ophthalmic Pathology Laboratory. Dr. Blodi, in whose honor the professorship is named, is internationally known for his teaching and research in ophthalmology. He served as head of the University of Iowa Department of Ophthalmology from 1967 to 1985.

**Barrett G. Haik**

Barrett G. Haik has been appointed the first recipient of the George M. Haik, Sr.-St. Giles Foundation Professorship of Pediatric and Adult Ophthalmic Oncology at Tulane University School of Medicine in New Orleans.

## INSTRUCTIONS TO AUTHORS

For the preparation of typescripts for THE AMERICAN JOURNAL OF OPHTHALMOLOGY

THE AMERICAN JOURNAL OF OPHTHALMOLOGY publishes original articles, letters, editorials, abstracts, book reviews, and news items. Editorials, book reviews, and abstracts are published by invitation. Timely articles and letters about original observations in clinical and basic ophthalmology are welcome. Each article submitted is evaluated by two or more scientific referees who recommend that the paper be (1) accepted as submitted, (2) returned for revision, or (3) rejected. Acceptance is determined by such factors as the originality, significance, and validity of the contribution, the suitability of the subject matter for subscribers to THE JOURNAL, and the editorial care with which the manuscript has been prepared.

One author should be designated as the corresponding author. This individual will be responsible for all questions about the preparation of the manuscript for publication. Authors are advised promptly of receipt of their papers. Within 45 days thereafter they are advised of acceptance, rejection, or the need for revision.

### Disclosure and Copyright Transfer

At the time of submission, a signed copy of the disclosure statement and copyright transfer published in THE JOURNAL each month must be included with the manuscript. No article or letter will be reviewed until this disclosure statement and copyright transfer, signed by each author in the order that each name appears on the title page, has been received. The transfer must also list the home address of each author and the telephone number of the corresponding author.

The manuscript must be original and may not contain data published previously or submitted for publication elsewhere. If the data were presented at a scientific meeting, the place, date of presentation, and auspices of the meeting should be stated on the title page.

### Mechanical Preparation of the Typescript

Submit an original and at least two duplicate copies of both the typescript and the illustrations. Xerographic copies of the typescript are preferred to carbon copies.

Use 8½ × 11-inch heavy, white, bond paper.

Provide 1½-inch margins on all four sides of each page and indent paragraphs ½ inch.

The entire typescript, including title page, quotations, footnotes, acknowledgment, references, legends, and tables, must be double-spaced.

Use black, legible type.

Use standard type.

Do not underline.

Do not use italics, cursive, condensed, boldface, expanded, or reduced type.

Use nothing smaller than 12 pitch or 11 point type.

Do not vary the type size.

Do not use all capitals.

Never use any single-spacing.

Do not justify right margins.

Do not use a dot matrix printer. The type must be letter quality with clear, unbroken characters that do not touch or overlap.

Number each page in the upper right-hand corner. List the first author's name and short title of the article (maximum, 60 characters and spaces) in the upper right-hand corner.

Spell out all terms except standard measurements used with numeric quantities, such as mm Hg, cm, and ml. Do not abbreviate or use acronyms.

Numeric equivalents must precede all percentages. For example: Of 80 patients, 20 (25%) had retinopathy.

All P values must be exact and not greater than or less than some value.

Prepare references, legends, and tables in THE JOURNAL style. (See following detailed instructions.)



## Original Articles

The manuscript should be arranged in the following order: Title page; Summary; Introductory text; Material and Methods, Subjects and Methods, or Case Reports; Results; Discussion; References; Legends for illustrations; and Tables.

**Title page.** The title page is page 1. It should contain the title, a brief heading (no more than 60 characters and spaces) in the upper right-hand corner, and each author's name with the highest (one only) academic degree. The department and the institution where the study was performed should be indicated. Sponsoring organizations and grant support are acknowledged on the title page.

Referring physicians, consultants, editorial assistants, photographers, artists, laboratory assistants, secretaries, and others who assist in preparation of a paper cannot be acknowledged, however valuable their services. Special statistical assistance may be acknowledged.

The name and mailing address of the author to whom requests for reprints should be directed must be indicated on the title page.

Each page that follows the title page must be numbered consecutively, and must include the first author's name and the brief title in the upper right-hand corner.

**Summary.** Each article must have a summary that specifically condenses the content of the paper in 150 words or less. It should include the main clinical or research data and findings but exclude speculation. The summary must be written so that the message of the paper can be understood independently. It may not contain references, illustrations, tables, or data not included in the text. It should not repeat or paraphrase the title. The summary should describe the following: why the study was done; who or what was studied; the results of the study; the significance of the study; and any recommendations based on the study.

**Narration.** Articles should be organized and prepared in the style used by THE JOURNAL. A brief introductory statement of the problem should be presented. Material and methods or the patient selection should then be described in enough detail for a reader to replicate the study. Results of the study should be given, followed by a discussion. The discussion elucidates the results and must relate directly to the topic of the paper.

**References.** THE JOURNAL does not publish extensive bibliographic reviews. References must be numbered consecutively, both in the text and in

the reference list. Reference numbers in the text must be typed as superscripts. The submitting author is responsible for complete and accurate references, including the proper capitalization and accent marks used in foreign-language publications.

Personal communications, posters, program abstracts, unpublished data, manufacturers' manuals, and oral discussions that the reader cannot retrieve should be kept to a minimum and must be incorporated into the text without reference numbers. References to studies that have been accepted but have not yet been published must indicate the publication in which they will be published. References to studies in preparation or submitted for publication are not allowed. Primary, not secondary, sources must be cited. References to books must contain inclusive pages of the section cited. The names of all authors must be cited in the reference list. THE JOURNAL does not use the term "et al." The names of all authors must be fully punctuated. The following style is used by THE JOURNAL for periodicals (1), for books (2), and for chapters in books (3).

1. Spoor, T. C., Kwitko, G. M., O'Grady, J. M., and Ramocki, J. M.: Traumatic hyphema in an urban population. *Am. J. Ophthalmol.* 109:23, 1990.

2. Harrington, D. O., and Drake, M. V.: The Visual Fields. Text and Atlas of Clinical Perimetry, ed. 6. St. Louis, C. V. Mosby, 1990, p. 156.

3. Abrams, G. A.: Retinotomies and retinectomies. In Ryan, S. J. (ed.): *Retina*, vol. 3. St. Louis, C. V. Mosby, 1989, pp. 321-322.

The originator of a personal communication must provide written permission to be quoted.

Abbreviations for periodicals are listed in *Index Medicus*: *Am. J. Ophthalmol.*, *Surv. Ophthalmol.*, *Br. J. Ophthalmol.*, and the like. If there is any doubt about an abbreviation, the full name of the publication should be spelled out.

**Illustrations.** Graphs, diagrams, and photographs must not be mounted. Each illustration should be numbered and cited consecutively in the text. The illustration number, an arrow indicating the top of the figure, and the first author's name should be indicated on a label on the back.

The figure number, legend, title, or text should not appear on the face of an illustration.

Graphs, diagrams, and line drawings must be prepared by a professional artist using India ink. Photographs must have a glossy finish and sharp contrast. Lettering, arrows, and the like must be professionally applied. In a series of illustrations, all parts should be oriented in the same direction. Photographs should be the same size or slightly larger than the intended reproductions. Figure widths in THE JOURNAL are 3 inches (one column)

and 6½ inches (two columns). Lettering must be planned with reductions to these sizes in mind; letters should be of uniform size and large enough to be read easily after reduction.

Photographs should be cropped to exclude non-pertinent material. The front of each photograph should be marked with a grease pencil to show the area to be reproduced.

THE JOURNAL does not use stereoscopic illustrations.

Each illustration must have a legend that describes the significance of what is shown. Legends should be typed consecutively on a page (separate from the illustrations themselves). Legends should be typed in the form used by THE JOURNAL, as follows:

Fig. 1 (Jones, Smith, and Brown). Histologic section of the left eye of Patient 1 shows infiltrating histiocytes (hematoxylin and eosin,  $\times 70$ ).

If there are more than three authors, use the name of the first author followed by "and associates."

If photographs of patients that include the eyes, nose, and mouth are submitted, the author must supply THE JOURNAL with proof of informed consent.

Individual illustrations and legends are preferred to composites made up of two or more separate parts. If multiple-part illustrations are submitted, they should be labeled from left to right and from top to bottom as follows:

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Visual field charts and charts for plotting Farnsworth-Munsell color testing used in THE JOURNAL will be supplied to authors on request without charge. Write to Editorial Assistant, American Journal of Ophthalmology, Suite 1415, 435 N. Michigan Ave., Chicago, IL 60611.

**Color.** Authors must contribute to the cost of color reproductions. The charge to authors for color is \$500 per page of color. Both color transparencies and high-quality color prints must be submitted with the paper, together with a layout indicating the proposed distribution of the illustrations and legends.

**Tables.** Each table must have a title and an arabic numeral. Tables must be cited consecutively in the text.

Each table must be double-spaced and nothing

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Vertical lines should not be used anywhere in the table.

All columns and rows should be labeled; lengthy descriptions belong in the text or as a footnote to the table, not in the table itself.

Diseases, disorders, and clinical findings may not be abbreviated, however lengthy their descriptions. Abbreviations may only be used to indicate units of measure. The following symbols are used for footnotes in the order indicated: \* (asterisk), † (dagger), ‡ (double dagger), § (section mark), || (parallels), ¶ (paragraph mark), and # (number sign).

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**Reprints.** Reprints must be ordered promptly. A reprint order form is sent to the corresponding author four to six weeks before publication of the article.

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Letters describe unusual clinical or pathologic findings, experimental results, and new instruments and techniques. Letter typescripts should be prepared in the same way as Original Articles. An original and two copies of the typescript and illustrations must be sent. The typescript must be no more than five pages in length (title page, two pages of text, reference page, and legend page). References must be limited to five. No more than two black-and-white illustrations, 3 inches wide (one column in width), may be used. Color illustrations cannot be used.

The Editorial Board either accepts or rejects letters. They are not returned with suggestions for revision. Because space limitations restrict the opportunity for an extended discussion or review, THE JOURNAL does not publish correspondence concerning letters.



## Correspondence

Correspondence about recent articles or other material published in *THE JOURNAL* should be submitted within six weeks of publication. Correspondence should be prepared in the same way as an Original Article and should be no more than two typewritten pages.

## News Items

*THE JOURNAL* welcomes information about meetings, honors, and appointments. Only one news item should be included on each page. News items should be double-spaced and provide the name, address, and telephone number of the individual

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*THE JOURNAL* recommends the following publications as guides to style, grammar, and spelling:

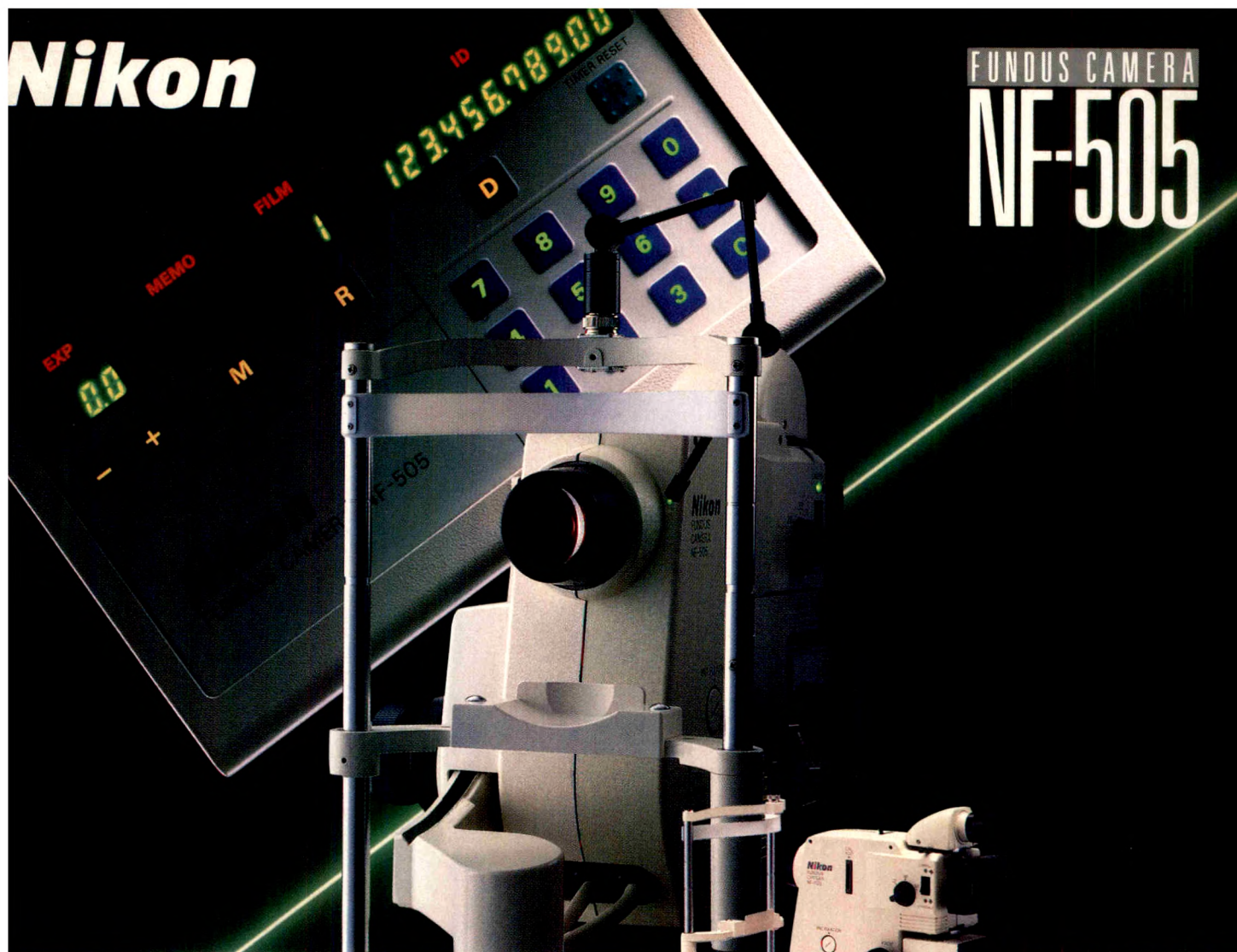
CBE Style Manual Committee: Council of Biology Editors Style Manual. A Guide for Authors, Editors and Publishers in the Biological Sciences, ed. 5. Bethesda, Council of Biology Editors, 1983.

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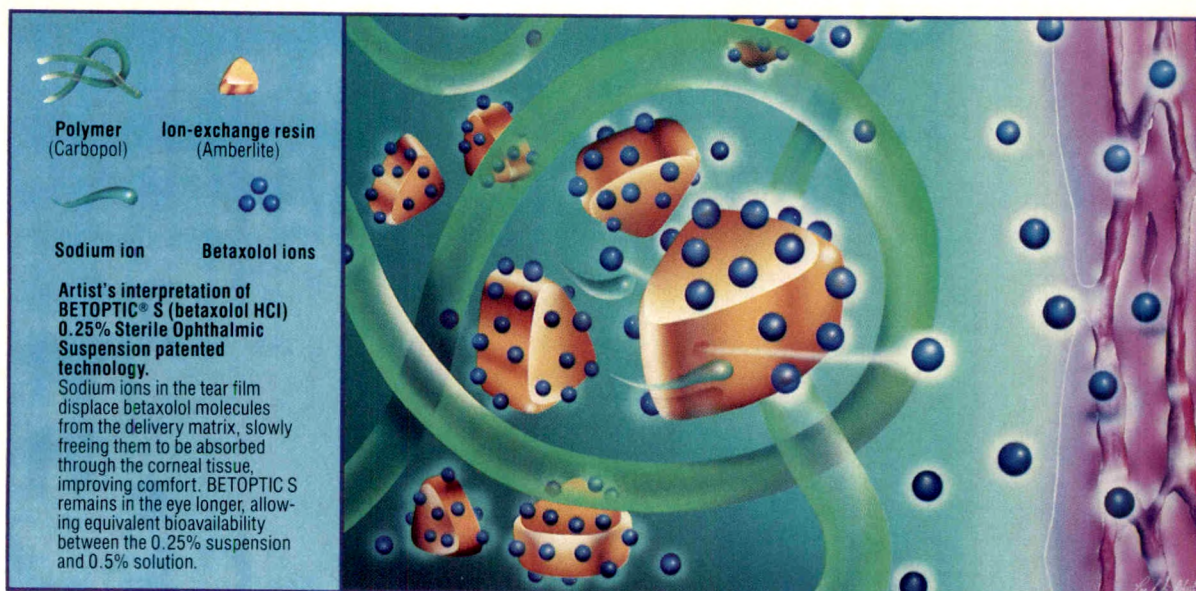
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**PRECAUTIONS: General: Diabetes Mellitus.** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrototoxicosis.** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

**Muscle Weakness.** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

**Major Surgery.** Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. **Pulmonary.** Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. **Drug Interactions:** Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. **Pregnancy: Pregnancy Category C.** Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS: Ocular:** In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, edema and anisocoria. **Systemic:** Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include: **Cardiovascular:** Bradycardia, heart block and congestive failure. **Pulmonary:** Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure. **Central Nervous System:** Insomnia, dizziness, vertigo, headaches, depression, and lethargy. **Other:** Hives, toxic epidermal necrolysis, hair loss, and glossitis.

**OVERDOSAGE:** No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. A topical overdose of BETOPTIC S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

**CAUTION: Federal (USA) Law Prohibits Dispensing Without a Prescription.**  
U.S. Patent Nos. 4,252,984; 4,311,708; 4,342,783; 4,911,920.

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## PRODUCTS AND SERVICES

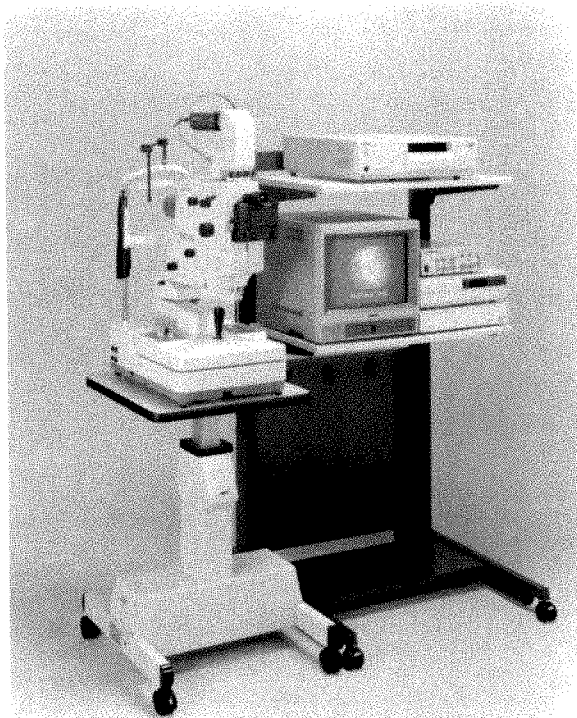
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*New products and services considered by the editors to be of interest to our readers are described on the basis of information supplied by the companies cited. Publication of these notices does not imply endorsement or warranty by The Ophthalmic Publishing Company, publishers of The American Journal of Ophthalmology, for these products and services.*

### ► Diagnostic Instruments

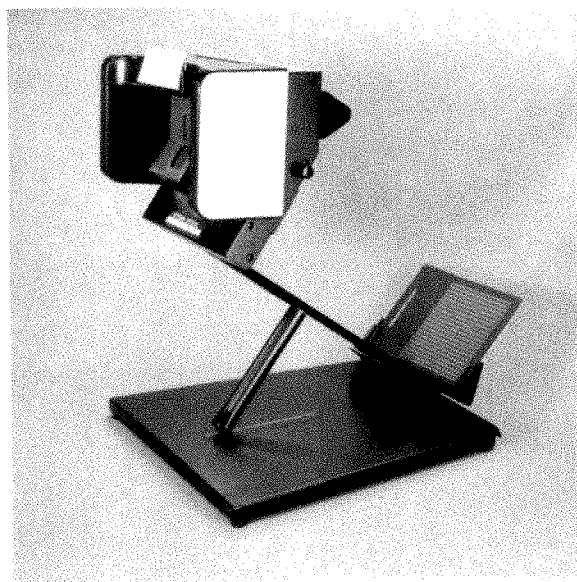
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**Topcon Instrument Corp. of America**  
65 W. Century Rd.  
Paramus, NJ 07652  
Tel: (201) 261-9450  
Fax: (201) 387-2710

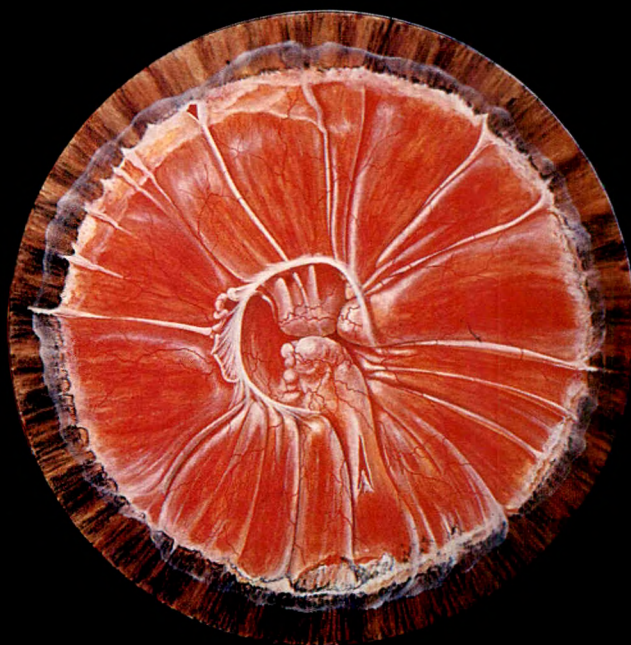


The TRC-501A, from Topcon Instrument Corporation of America is a compact and integrated instrument capable of switching between three types of fundus photography: choroidal infrared fluorescein angiography, color fundus photography, and fluorescein fundus angiography. Once changed, the operative filters automatically adapt the camera to the proper mode. Another feature of the TRC-501A is its ability to permeate choroidal capillaries. The power supply and optical system are integrated into a single, compact component.

**Stereo Optical Company**  
3539 N. Kenton Ave.  
Chicago, IL 60641  
Tel: (800) 344-9500 (National)  
(312) 777-2869 (Chicago)



Stereo Optical introduced its table model of the threshold Amsler grid (TA-300). The threshold Amsler grid offers an extremely sensitive evaluation of the central 10 degrees of the visual field. The test takes less than two minutes to complete. Additionally, the unit incorporates its own lighting system, allowing the tester to control all test variables better. The TA-300 is calibrated to allow measurement of the angle of polarization for easy tracking of vision degradation and rapid reproduction of testing conditions in follow-up visits.



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## ► Pharmaceuticals

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**CooperVision Pharmaceuticals**  
**3495 Winton Place**  
**Rochester, NY 14623**  
**Tel: (800) 225-2578 (National)**  
**(716) 427-7960 (New York)**

CooperVision Pharmaceuticals, Inc., announced the launch of the Eyescrub line. Eyescrub is a cleanser specifically formulated for the hygienic management of blepharitis. The patented Eyescrub formulation is a mild, hypoallergenic cleanser that is specifically intended for use in the periocular area. Eyescrub provides the health-care professional with an alternative to the use of baby shampoos in the management of blepharitis. The Eyescrub product line consists of the Eyescrub kit, a 4-oz (120-ml) bottle and 60 cleansing pads; a 4-oz bottle refill; a 100-cleansing pad box; 15-ml special packs.

---

**Storz Ophthalmics**  
**3365 Tree Court Industrial Blvd.**  
**St. Louis, MO 63122-6694**  
**Tel: (314) 225-5051**  
**Fax: (314) 225-7365**

Rêv-Eyes (dapiprazole HCl), a new agent that rapidly reverses the effects of diagnostic mydriasis (pupillary dilation) induced by phenylephrine and tropicamide, is now available. The dosage for Rêv-Eyes is two drops in each dilated eye followed by two more drops five minutes later. The effects of the dilating agent will start to reverse shortly thereafter. Although complete reversal may take about two hours, most patients treated with Rêv-Eyes will have significantly less-dilated pupils within 30 minutes to an hour.

## ► Diagnostic Lenses

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**Volk Optical**  
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**Mentor, OH 44060**  
**Tel: (800) 345-VOLK (National)**  
**(216) 942-6161 (Ohio)**



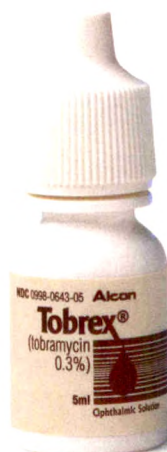
Volk Optical has a new higher magnification, wide-field fundus/laser contact lens, the Area Centralis lens. This lens is designed specifically for detailed examination and treatment in the central retinal area. The new lens complements the super-wide field QuadrAspheric fundus lens introduced in 1990. The Area Centralis lens is available with Volk's AR/DI laser coating for diode laser. AR/DI laser coating provides high antireflection characteristics within the visible spectrum as well as peak performance for argon (488/512 nm) and infrared diode (810 nm) lasers.



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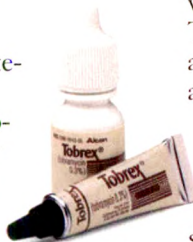


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## TOUGH ON PATHOGENS, GENTLE ON PATIENTS

In treating ocular infection, TOBREX® (tobramycin 0.3%) is the one word that says it all. Other antibiotics that work bacteriostatically merely inhibit the growth of common ocular pathogens. TOBREX actually *destroys* them. Because it is bactericidal and offers broad spectrum coverage, and because it provides superior patient comfort, TOBREX is the most widely



prescribed ocular antibiotic worldwide. In fact, many regard TOBREX as the “gold standard” against which other antibiotics are measured.

When prescribing for ocular infection, you want bactericidal action, broad spectrum coverage, and superior patient comfort. Remember the one word that says it all. Prescribe TOBREX.

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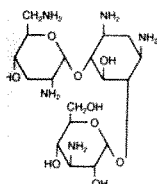
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FORT WORTH, TEXAS 76134

**Tobrex®**

**(tobramycin 0.3%)**

Ophthalmic Solution  
and Ointment

**DESCRIPTION:** TOBREX® (tobramycin 0.3%) is a sterile topical ophthalmic antibiotic formulation prepared specifically for topical therapy of external infections. This product is supplied in solution and ointment forms. Each mL of solution contains: Active: tobramycin 0.3% (3 mg). Preservative: Benzalkonium Chloride 0.01% (0.1 mg). Inactive: oric Acid, Sodium Sulfate, Sodium Chloride, Tyloxapol, Sodium Hydroxide and/or Sulfuric acid (to adjust pH) and Purified Water. DM-00 Each gram of ointment contains: Active: Tobramycin 0.3% (3 mg). Preservative: Chlorbutanol 0.5% (5 mg). Inactive: Mineral Oil and White Petrolatum. DM-00 Tobramycin is a water-soluble aminoglycoside antibiotic active against a wide variety of gram-negative and gram-positive ophthalmic pathogens. The chemical structure of tobramycin is:



Chemical name  
{3-amino-3-deoxy-α-D-  
uco-pyranosyl-(1→4)}-  
2,6-diamino-2,3,6-  
deoxy-α-D-ribohexo-  
uranosyl-(1→6)}-2-  
deoxystreptamine.

**CLINICAL PHARMACOLOGY:** In Vitro Data: In vitro studies have demonstrated tobramycin is active against susceptible strains of the following microorganisms: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, and *Acinetobacter calcoaceticus* and some *Neisseria* species. Bacterial susceptibility studies demonstrate that in some cases, microorganisms resistant to gentamicin retain susceptibility to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

**INDICATIONS AND USAGE:** TOBREX is a topical antibiotic indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of TOBREX. Clinical studies have shown tobramycin to be safe and effective for use in children.

**CONTRAINDICATIONS:** TOBREX Ophthalmic Solution and Ointment are contraindicated in patients with known hypersensitivity to any of their components.

**WARNINGS:** NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to TOBREX occurs, discontinue use.

**PRECAUTIONS:** General. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Ophthalmic ointments may retard corneal wound healing.

**Information For Patients:** Do not touch dropper or tube tip to any surface, as this may contaminate the contents.

**Pregnancy Category B.** Reproduction studies in three types of animals at doses up to thirty-three times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the fetus due to tobramycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers.** Because of the potential for adverse reactions in nursing infants from TOBREX, a decision should be made whether to discontinue nursing the infant or to discontinue the drug, taking into account the importance of the drug to the mother.

**ADVERSE REACTIONS:** The most frequent adverse reactions to TOBREX Ophthalmic Solution and Ointment are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than three of 10 patients treated with TOBREX. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported from TOBREX therapy; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

In clinical trials, TOBREX Ophthalmic Ointment produced significantly fewer adverse reactions (3.7%) than did GARAMYCIN® Ophthalmic Ointment (10.6%).

**OVERDOSAGE:** Clinically apparent signs and symptoms of an overdose of TOBREX Ophthalmic Solution or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

#### USAGE AND ADMINISTRATION:

**Solution:** In mild to moderate disease, instill one or two drops into the affected eye(s) every four hours. In severe infections, instill two drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.

**Ointment:** In mild to moderate disease, apply a half-inch ribbon into the affected eye(s) two or three times per day. In severe infections, instill a half-inch ribbon into the affected eye(s) every three to four hours until improvement, following which treatment should be reduced prior to discontinuation.

TOBREX ointment may be used in conjunction with TOBREX solution.

**HOW SUPPLIED:** 5 mL sterile solution in DROP-TAINER® dispenser (NDC 0998-0643-05), containing tobramycin 0.3% (3 mg/mL) and 3.5 g sterile ointment in ophthalmic tube DC 0065-0644-35), containing tobramycin 0.3% (3mg/g).

**ORAGE:** Store at 46° - 80°F.

**UTION:** Federal (USA) law prohibits dispensing without prescription.

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Eagle Laboratories has added a 27GA silicone "squeegee" capsule polisher to its line of single use, disposable ophthalmic instruments. The smaller gauge instrument features the same dimensions as the 23GA version, with a 7-mm bend to tip and a 7-mm long silicone sleeve extending approximately 1 mm beyond the cannula tip. An additional use for this silicone-tipped instrument is to manipulate the intraocular lens during insertion.

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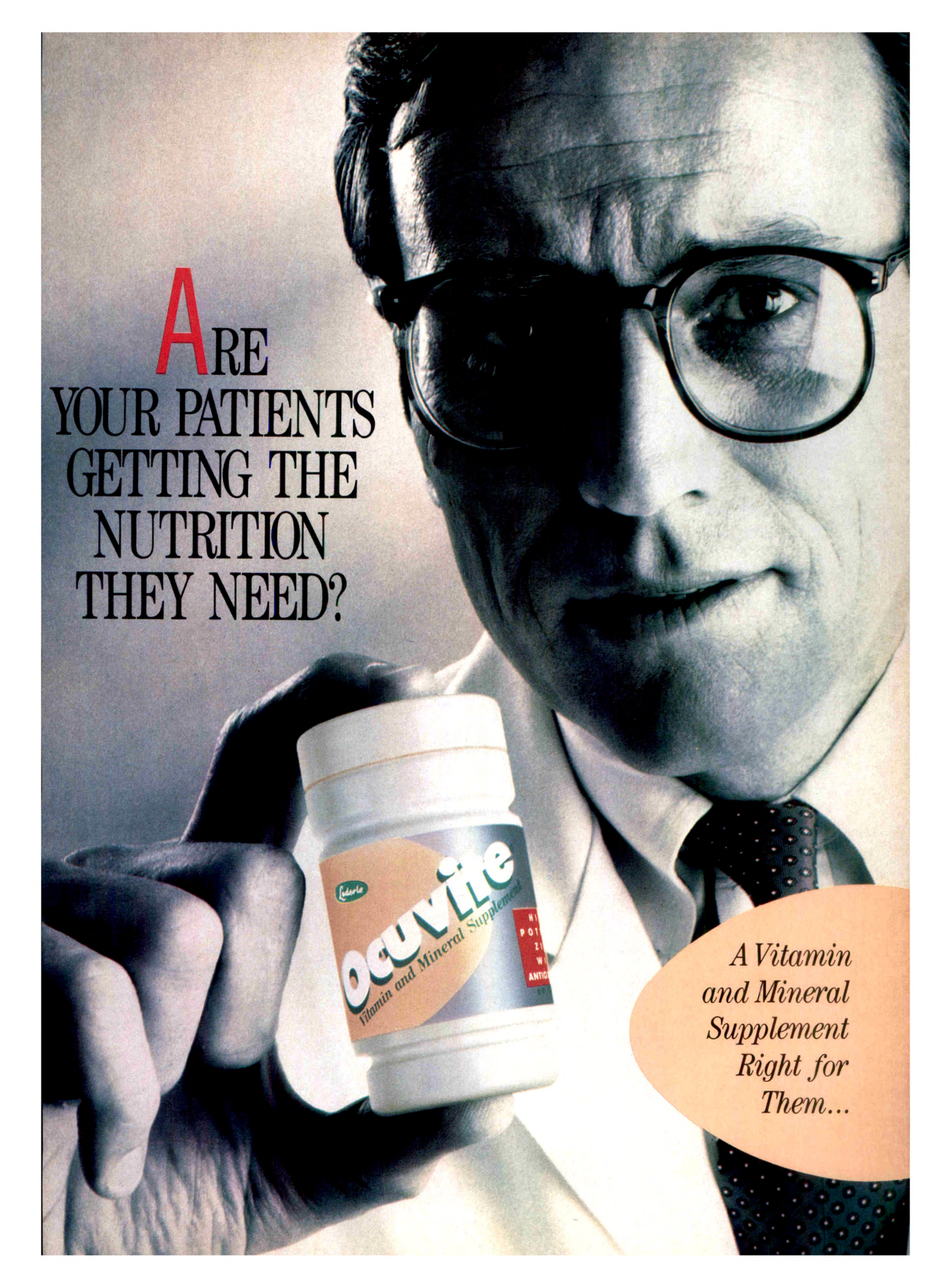


A new, powder-free latex glove designed for use in cleanrooms and other clean environments is distributed by Thomas West, Inc. These gloves have been case-hardened, cleaned to Class 100 status and have passed rigid particulate and extractables testing.

A unique microtexture, or bisque, finish ensures a secure grip on even extremely small items. The natural latex gloves have a thickness of 7 mils; the 12-inch length provides maximum protection for hands and wrists. Glove tensile strength is 3400 psi with 785% minimum elongation.

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Micronutrient	Zinc 40mg (elemental)	Vitamin C 60mg	Vitamin E 30 IU	Vitamin A 5000 IU (as Beta Carotene)	Copper 2mg (elemental)	Selenium 40mcg
Percent US RDA for Adults	267%	100%	100%	100%	100%	No US RDA established
Micronutrient Sources in Balanced Diets	Oysters, red meat, liver, soybeans, spinach, sunflower seeds	Citrus fruits, tomatoes	Eggs, organ meats, wheat germ, dark green vegetables, legumes	Dairy products, green and yellow fruits and vegetables, fish liver oil	Legumes, organ meats, seafood, nuts	Eggs, garlic, leafy green vegetables, liver, seafood, bran

**RECOMMENDED INTAKE:** Adults: One tablet, one or two times daily or as directed by physician.

**References:** 1. Pennington JAT, Young BE, Wilson DE, Johnson RD, Vanderveen JE. Mineral content of foods and total diets: The Selected Minerals in Foods Survey, 1982 to 1984. *J Am Diet Assoc.* 1986;86:876-878. 2. Fanelli MT, Steinhagen KJ. Characterizing consumption patterns by food frequency methods: core foods and variety of foods in diets of older Americans. *J Am Diet Assoc.* 1985;85:1570-1576. 3. *Red Book*® Update. Oradell, NJ: Medical Economics Co Inc, 1990;July:48.

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**VITREORETINAL SURGEON:** Growing multi-doctor medical and surgical retina only referral practice desires an associate leading to partnership. Practice is well established with excellent facilities and equipment. Quality retinal fellowship required. Reply with C.V. to Box 222 AJO.

**VITREORETINAL SURGEON:** Prestigious, seven doctor, retina only, referral practice seeks associate leading to partnership. Private practice with academic affiliation. Send C.V. in confidence to Box 221 AJO.

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- Director of Section—Board certified ophthalmologist trained and experienced in all aspects (surgical/research) of retina and vitreous diseases. Will be expected to direct teaching, research, and clinical programs.
- Assistant Professor—Ophthalmologist (BC/BE) retina-vitreous vascular specialty training. Seeking highly motivated individual with demonstrated involvement in quality research, clinical service and teaching.

Qualified candidates should forward a letter of interest and C.V. with bibliography to: Chairman, Search Committee, Department of Ophthalmology & Visual Science, Yale University School of Medicine, P.O. Box 3333, New Haven, CT 06510.

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**VITRO-RETINAL SURGEON:** Dynamic medical/surgical retina vitreous only practice in large mid-western city seeks fellowship trained vitreo-retinal surgeon. Academic affiliation available. BE/BC. Send C.V. to Box 227 AJO.

**POSITIONS WANTED**

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## Polytrim® Ophthalmic Solution Sterile (trimethoprim sulfate and polymyxin B sulfate)

**INDICATIONS AND USAGE:** Polytrim Ophthalmic Solution is indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharoconjunctivitis, caused by susceptible strains of the following microorganisms: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Haemophilus influenzae* and *Pseudomonas aeruginosa*. \* Efficacy for this organism in this organ system was studied in fewer than 10 infections. **CONTRAINDICATIONS:** Polytrim Ophthalmic Solution is contraindicated in patients with known hypersensitivity to any of its components. **WARNINGS:** NOT FOR INJECTION INTO THE EYE. If a sensitivity reaction to Polytrim occurs, discontinue use. Polytrim Ophthalmic Solution is not indicated for the prophylaxis or treatment of ophthalmia neonatorum. **PRECAUTIONS:** **General:** As with other antimicrobial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. **Information for Patients:** Avoid contaminating the applicator tip with material from the eye, fingers, or other source. This precaution is necessary if the sterility of the drops is to be maintained. If redness, irritation, swelling or pain persists or increases, discontinue use immediately and contact your physician. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** **Carcinogenesis:** Long-term studies in animals to evaluate carcinogenic potential have not been conducted with polymyxin B sulfate or trimethoprim. **Mutagenesis:** Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels after oral administration; at concentrations approximately 1000 times human plasma levels after oral administration in these same cells a low level of chromosomal damage was induced at one of the laboratories. Studies to evaluate mutagenic potential have not been conducted with polymyxin B sulfate. **Impairment of Fertility:** Polymyxin B sulfate has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown. No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females. **Pregnancy:** **Teratogenic Effects:** **Pregnancy Category C.** Animal reproduction studies have not been conducted with polymyxin B sulfate. It is not known whether polymyxin B sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Trimethoprim has been shown to be teratogenic in the rat when given in oral doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with oral doses 6 times the human therapeutic dose. While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell, in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or oral trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter. Because trimethoprim may interfere with folic acid metabolism, trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival. **Pediatric Use:** Safety and effectiveness in children below the age of 2 months have not been established (see WARNINGS). **ADVERSE REACTIONS:** The most frequent adverse reaction to Polytrim Ophthalmic Solution is local irritation consisting of transient burning or stinging, itching or increased redness on instillation. 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1. Ashley KC. The antimicrobial activity of topical anti-infective eye preparations. *Med Lab Sci* 1986;43:157-162.

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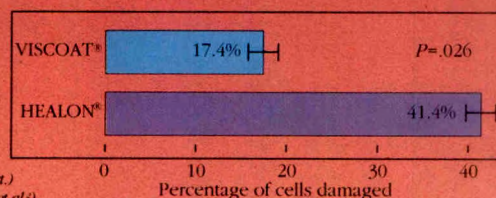
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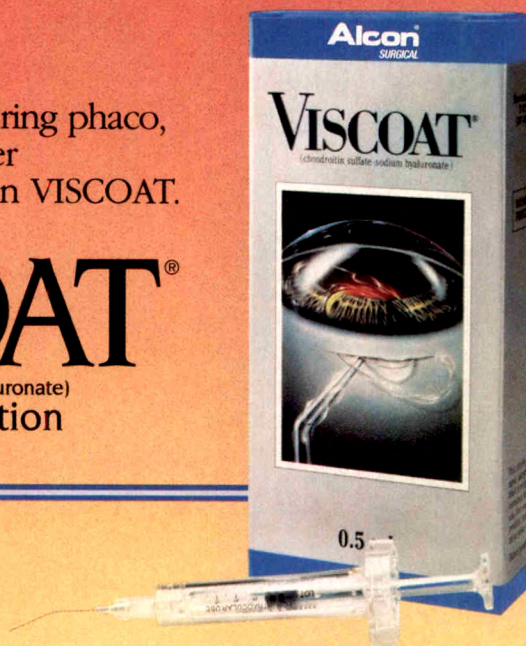
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**References**  
1. Sig MT, Olson RJ, Mamalis N, Olson RJ. Air bubble endothelial damage during phacoemulsification in human eye bank eyes: The protective effects of Healon and Viscoat. *J Cataract Refract Surg.* 1990;16:597-602.

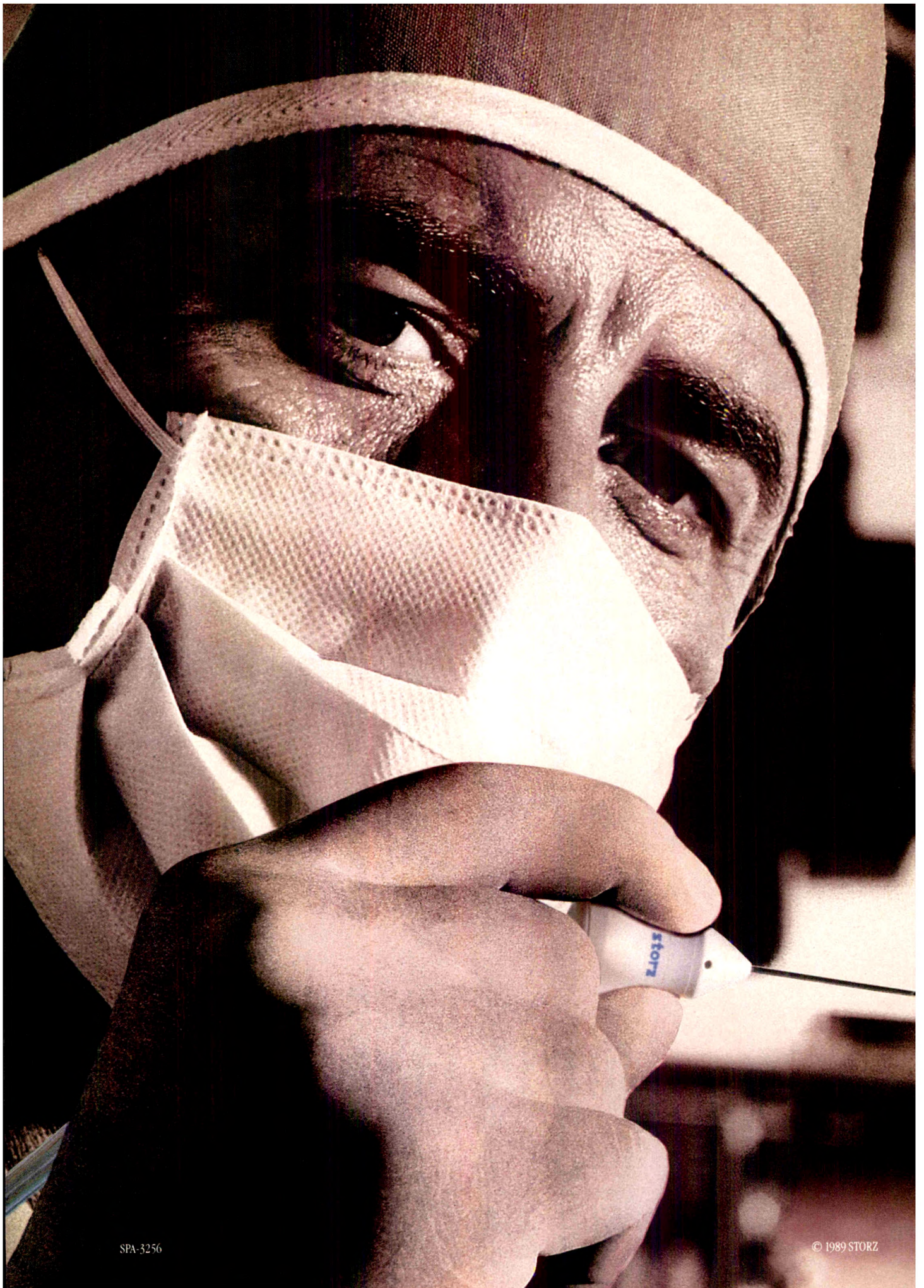
2. Glasser DB, Katz HR, Boyd JE, Langdon JD, Shobe SL, Peiffer RL. Protective effects of viscous solutions in phacoemulsification and traumatic lens implantation. *Arch Ophthalmol.* 1989;107:1047-1051.

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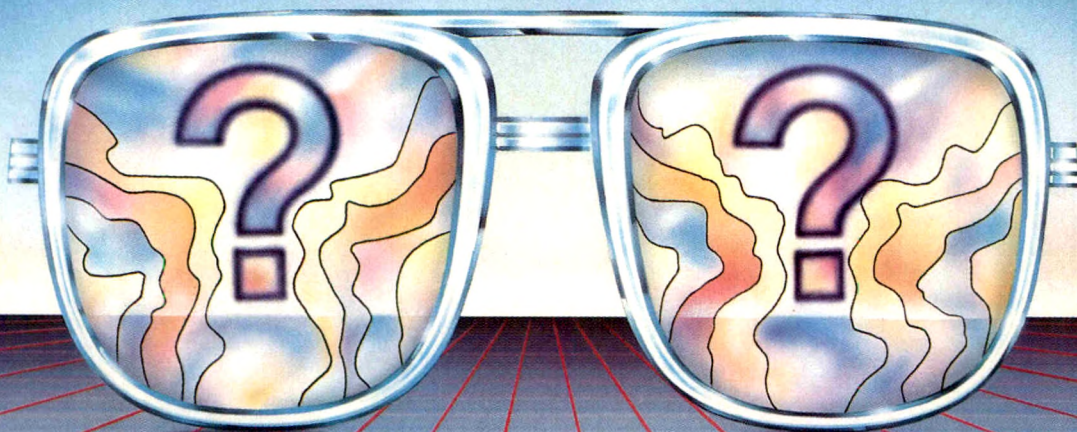


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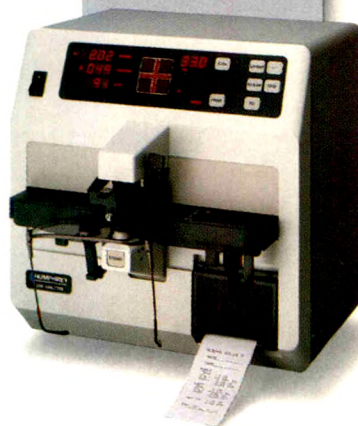
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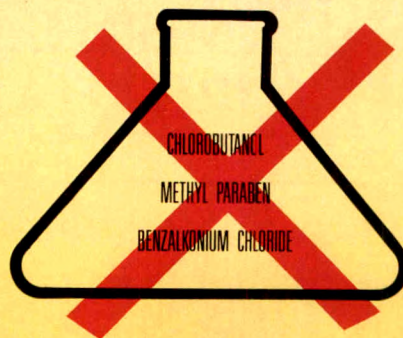
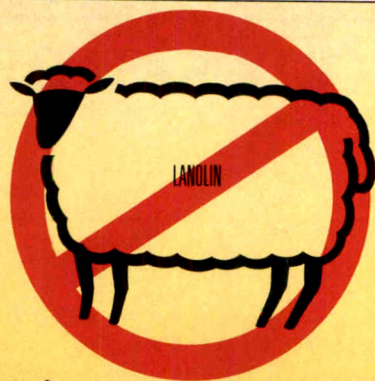
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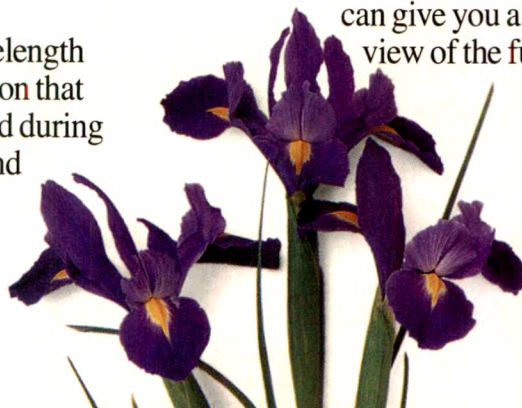


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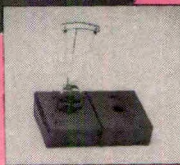
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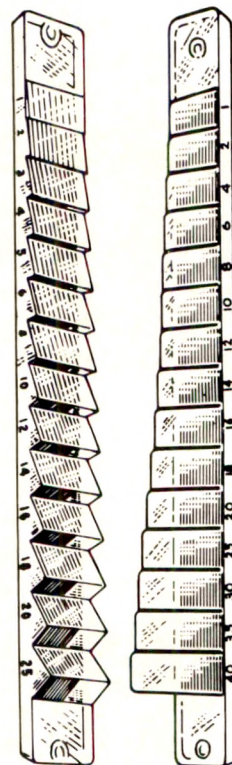
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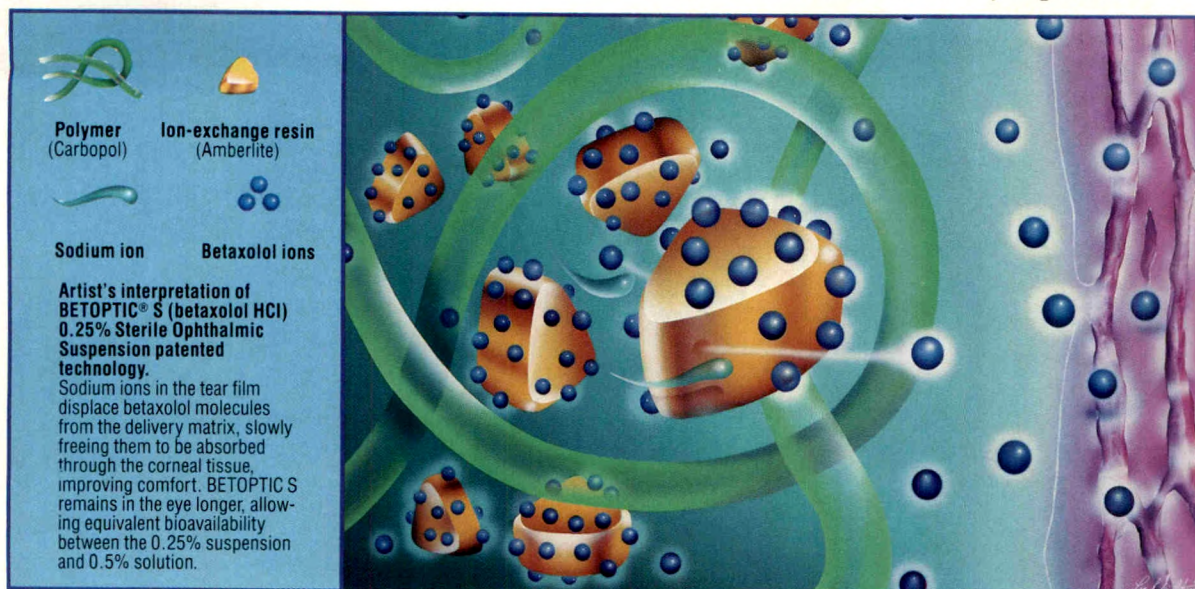
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**PRECAUTIONS: General: Diabetes Mellitus.** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrotoxicosis.** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

**Muscle Weakness.** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

**Major Surgery.** Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. **Pulmonary.** Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. **Drug Interactions:** Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. **Pregnancy: Pregnancy Category C.** Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children have not been established.

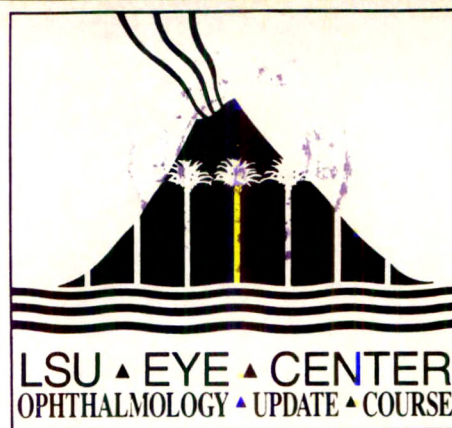
**ADVERSE REACTIONS: Ocular:** In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, edema and anisocoria. **Systemic:** Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include: **Cardiovascular:** Bradycardia, heart block and congestive failure. **Pulmonary:** Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure. **Central Nervous System:** Insomnia, dizziness, vertigo, headaches, depression, and lethargy. **Other:** Hives, toxic epidermal necrolysis, hair loss, and glossitis.

**OVERDOSAGE:** No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. A topical overdose of BETOPTIC S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

**CAUTION: Federal (USA) Law Prohibits Dispensing Without a Prescription.**  
U.S. Patent Nos. 4,252,984; 4,311,708; 4,342,783; 4,911,920.

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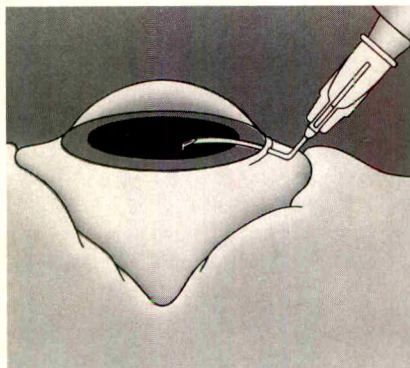


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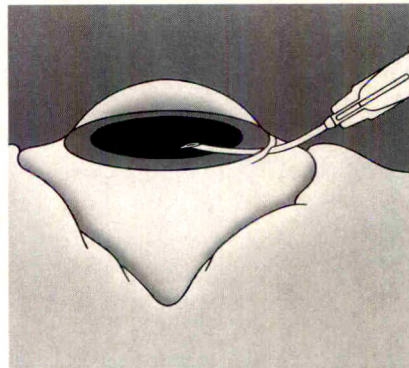
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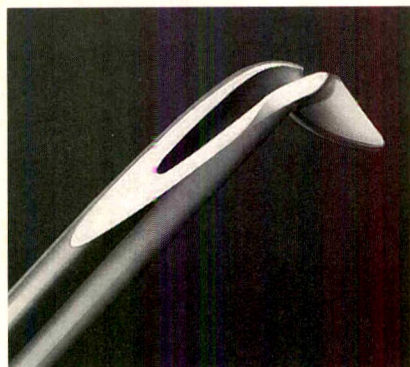
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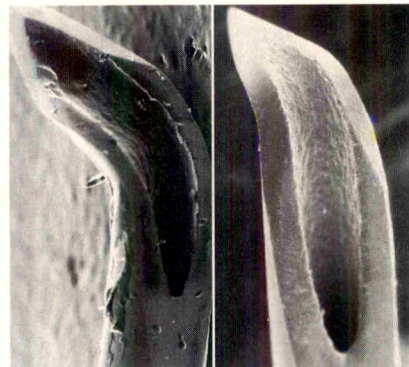
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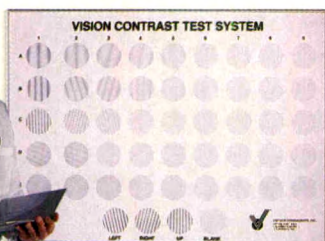
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# The Night Before

**Diamox® Sequels®**  
**acetazolamide**  
Sustained Release Capsules 500 mg



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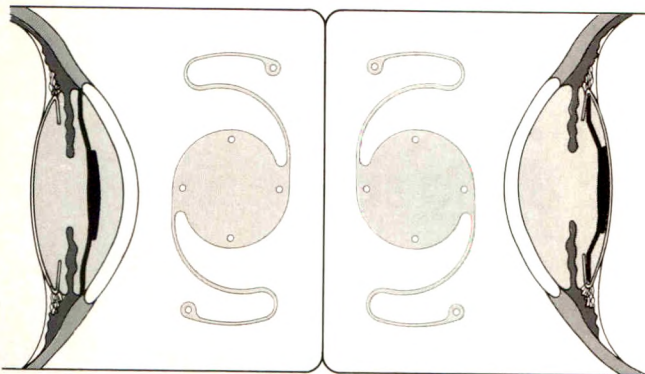
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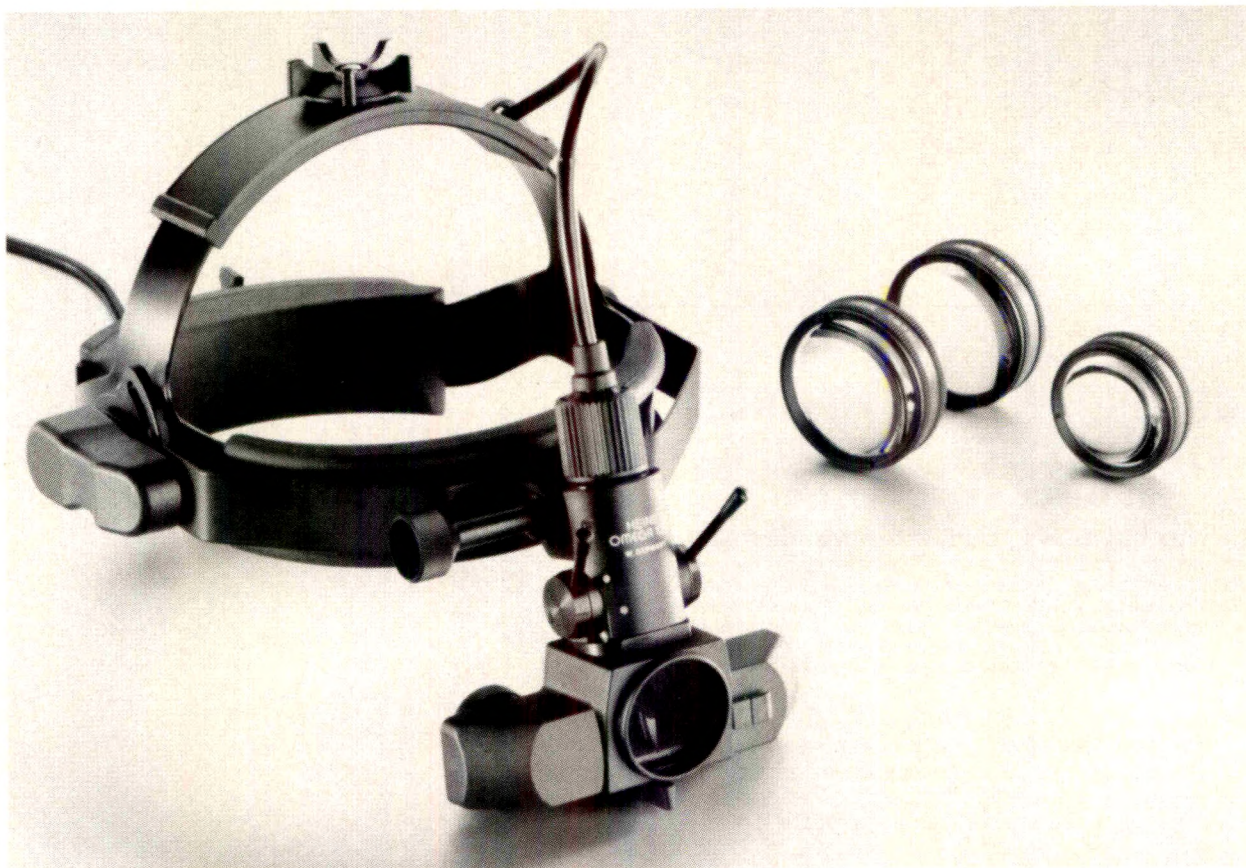
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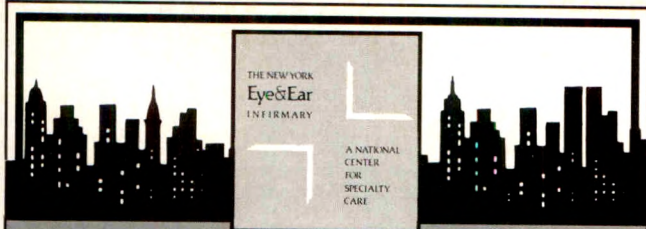
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**acetazolamide**  
Sustained Release Capsules 500 mg



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## Diamox Sequels

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## Diamox® Parenteral

sterile acetazolamide sodium

### Brief Summary

**DIAMOX® acetazolamide SEQUELS®, Tablets and Parenteral**

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**INDICATIONS:** *Tablets and Parenteral only:* For adjunctive treatment of edema due to congestive heart failure; drug-induced edema; centrencephalic epilepsies (petit mal, unlocalized seizures); forms: chronic simple (open-angle) glaucoma, secondary glaucoma and preoperatively in acute angle-closure glaucoma where delay surgery is desired in order to lower intraocular pressure. For prevention or amelioration of acute mountain sickness symptom climbers attempting rapid or gradual ascent.

### CONTRAINDICATIONS

When sodium and/or potassium serum levels are depressed, marked kidney and liver disease or dysfunction, including cirrhosis, supranal gland failure, and hyperchloremic acidosis. Long-term use in chronic noncongestive angle-closure glaucoma.

### WARNINGS

DIAMOX can cause fetal harm when administered to pregnant women. There have been reports of premature delivery and congenital anomalies. Administered orally or parenterally, DIAMOX has been shown to be teratogenic (defects of limbs) in mice, rats, rabbits, and rabbits. If used during pregnancy, or if the patient becomes pregnant while taking DIAMOX, she should be apprised of the potential hazard to the fetus.

Fatalities have occurred (rarely) due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitizations may recur when administered, irrespective of administration route. Discontinue use in signs of hypersensitivity or other serious reactions occur.

Caution is advised for patients on concomitant high-dose aspirin as anorexia, tachypnea, lethargy, coma, and death have been reported.

### PRECAUTIONS

Increasing the dose may increase drowsiness and paresthesia; decrease diuresis.

**Information for Patients:** Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, agranulocytosis. Early detection is advised and, if occurs, discontinue drug and institute appropriate therapy. Use caution in patients with pulmonary obstruction or emphysema. DIAMOX use does not obviate the need for prompt descent if symptoms of high altitude sickness occur.

Caution is advised for patients receiving concomitant high-dose aspirin and DIAMOX, as anorexia, tachypnea, lethargy, coma, and death have been reported (see **WARNINGS**).

**Laboratory Tests:** To monitor for hematologic reactions common to all sulfonamides, obtain baseline CBC and platelet count before beginning DIAMOX therapy and at regular intervals during the therapy. If significant changes occur, discontinue and institute appropriate therapy. Monitor for serum electrolytes.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term animal studies to evaluate the carcinogenic potential of DIAMOX have been conducted. In a bacterial mutagenicity test, DIAMOX was not mutagenic when evaluated with and without metabolic activation. The drug had no effect on fertility when given in the diet to male and female rats at a daily intake of up to 4 times the maximum recommended human dose of 1000 mg in a 50 kg individual.

**Pregnancy:** *Pregnancy Category D:* (See **WARNINGS**.)

**Nursing Mothers:** Because of potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug.

**Pediatric Use:** The safety and effectiveness of DIAMOX in children have not been established.

### ADVERSE REACTIONS

Short-term therapy: paresthesia, particularly a "tingling" feeling in the extremities; some loss of appetite, polyuria, drowsiness, confusion, tinnitus, taste alteration, and GI disturbances such as nausea, vomiting, and diarrhea. Metabolic acidosis and electrolyte imbalance may occur. Transient myopia has been reported, but subsides after drug is discontinued. Other: (occasional) urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, convulsions. Fatalities have occurred (rarely) due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias (see **WARNINGS**).

### OVERDOSAGE

No data are available regarding DIAMOX overdosage in humans. Animal data suggest that it is remarkably nontoxic. No specific antidote is known. Treatment should be symptomatic and supportive. See complete **OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** in package insert.

Rev

Manufactured for **STORZ**  
**STORZ OPHTHALMICS, INC.**  
St. Louis, Missouri 63122

By **LEDERLE LABORATORIES**  
A Division of American Cyanamid Corp.  
Pearl River, NY 10965



*The first fluoroquinolone for both bacterial conjunctivitis and corneal ulcer*

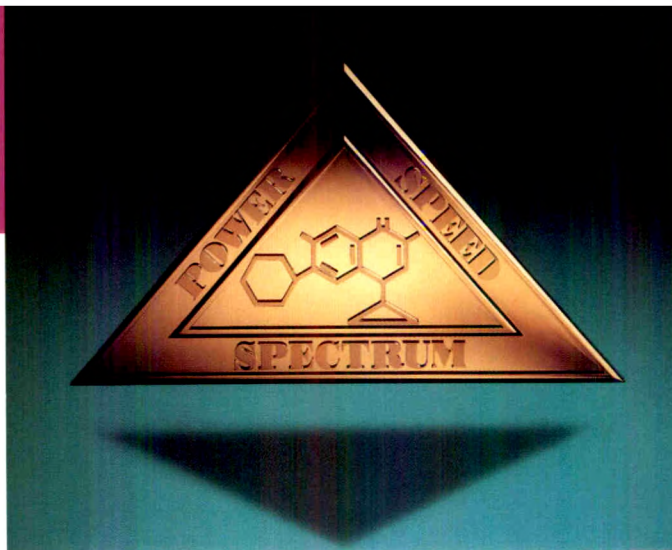
# **Ciloxan<sup>TM</sup>**

(ciprofloxacin HCl) 0.3% as Base  
Sterile Ophthalmic Solution

***Rapid killing action for  
important ocular pathogens***







# **Ciloxan<sup>TM</sup>**

(ciprofloxacin HCl) 0.3% as Base  
Sterile Ophthalmic Solution

***Rapid killing action for  
important ocular pathogens***

## **SPEED**

*Rapid resolution of ocular infections*

## **POWER**

*The power to treat both routine and tough ocular infections*

## **SPECTRUM**

*A broad spectrum of activity against important ocular pathogens*

# THE FIRST OF A STRONG NEW CLASS

**Powerful enough to achieve impressive results for bacterial conjunctivitis after only 7 days**

CILOXAN is microbiologically and clinically effective in lessening the intensity and shortening the duration of bacterial conjunctivitis.

#### Frequently Isolated Causative Organisms

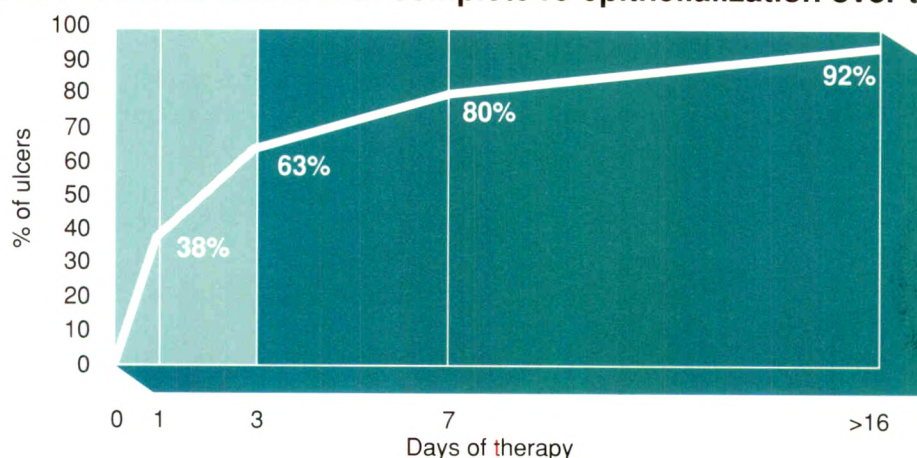
*Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Streptococcus pneumoniae*

#### Patients with Complete Eradication

78%  
76%  
75%

**After only 3 days of therapy, 63% of corneal ulcers were completely re-epithelialized**

Percent of corneal ulcers with complete re-epithelialization over time (n=148)



## THE POWER TO SUCCEED AS SINGLE-AGENT THERAPY

Clinical success for corneal ulcer patients was achieved using CILOXAN as single-agent therapy, without any fortified, systemic, or subconjunctival injections or other topical therapy. In clinical trials, resolution of bacterial infection and complete corneal re-epithelialization were achieved in 92% of patients with single-agent CILOXAN therapy.



# THE FIRST OF A STRONG NEW CLASS

## Broad spectrum coverage and potent in vitro activity

**CILOXAN is effective against these important ocular pathogens clinically and in vitro:**

Important Ocular Pathogens	MIC <sub>90</sub> (μg/mL)
<i>Pseudomonas aeruginosa</i>	0.72
<i>Serratia marcescens</i>	0.45
<i>Staphylococcus aureus</i>	0.70
<i>Staphylococcus epidermidis</i>	0.40
<i>Streptococcus pneumoniae</i>	2.60
<i>Streptococcus</i> (Viridans Group)	1.60

**CILOXAN is active against these organisms in vitro\*:**

Important Ocular Pathogens	MIC <sub>90</sub> (μg/mL)
<i>Hemophilus influenzae</i>	0.05
<i>Acinetobacter calcoaceticus</i>	0.54
<i>Chlamydia trachomatis</i>	1.00
<i>Citrobacter</i> species	0.22
<i>Enterobacter</i> species	0.27
<i>Escherichia coli</i>	0.12
<i>Klebsiella pneumoniae</i>	0.85
<i>Mycobacterium tuberculosis</i>	0.74
<i>Neisseria</i> species	0.01
<i>Proteus</i> species	0.05

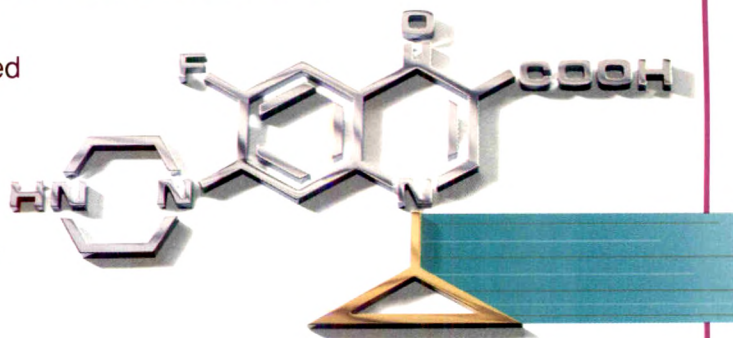
\*The clinical significance of these in vitro data is unknown.

## CIPROFLOXACIN HAS EXHIBITED A LOW FREQUENCY OF RESISTANCE

CILOXAN destroys bacteria differently through inhibition of the DNA gyrase. Only chromosomal mutation has been identified as a possible cause of bacterial resistance. CILOXAN does not cross-react with other types of antimicrobial agents such as beta-lactams or aminoglycosides, so organisms resistant to these drugs may be susceptible to CILOXAN.

## THE CILOXAN DIFFERENCE

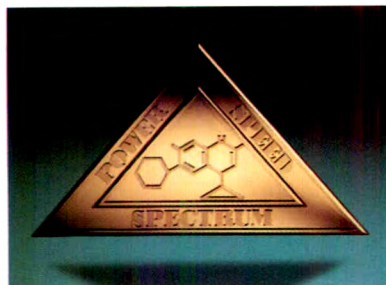
Spectrum, power, and speed are enhanced by a difference in chemical structure. CILOXAN is truly unique in its chemical structure. CILOXAN is the only fluoroquinolone with a cyclopropyl group which increases the overall potency of the drug.



Please see brief summary of prescribing information on the next page.

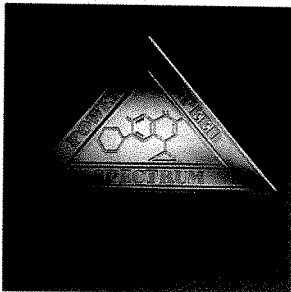
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OPHTHALMIC  
ALCON LABORATORIES, INC.  
FORT WORTH, TEXAS 76134

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**Rapid killing action for  
important ocular pathogens**

**Ciloxan**<sup>™</sup>  
(ciprofloxacin HCl) 0.3% as Base  
Sterile Ophthalmic Solution



# Ciloxan™

(ciprofloxacin HCl) 0.3% as Base  
Sterile Ophthalmic Solution

**DESCRIPTION:** CILOXAN™ (Ciprofloxacin HCl) Ophthalmic Solution is a synthetic, sterile, multiple dose, antimicrobial for topical ophthalmic use.

**INDICATIONS AND USAGE:** CILOXAN™ Ophthalmic Solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

**Corneal Ulcers:** *Pseudomonas aeruginosa*  
*Serratia marcescens*\*  
*Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Streptococcus pneumoniae*  
*Streptococcus* (Viridans Group)\*

**Conjunctivitis:** *Staphylococcus aureus*  
*Staphylococcus epidermidis*  
*Streptococcus pneumoniae*\*

\*Efficacy for this organism was studied in fewer than 10 infections.

**CONTRAINDICATIONS:** A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

**WARNINGS:** NOT FOR INJECTION INTO THE EYE.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

#### PRECAUTIONS:

**General:** As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.

In clinical studies of patients with bacterial corneal ulcer, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In one patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24-72 hours), in five patients, resolution was noted in 10-13 days. In nine patients, exact resolution days were unavailable; however, at follow-up examinations; 18-44 days after onset of the event, complete resolution of the precipitate was noted. In three patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome. (SEE ADVERSE REACTIONS).

**Drug Interactions:** Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives and has been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

*Salmonella*/Microsome Test (Negative)  
*E. coli* DNA Repair Assay (Negative)  
Mouse Lymphoma Cell Forward Mutation Assay (Positive)  
Chinese Hamster V<sub>79</sub> Cell HGPRT Test (Negative)  
Syrian Hamster Embryo Cell Transformation Assay (Negative)  
*Saccharomyces cerevisiae* Point Mutation Assay (Negative)  
*Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)  
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay  
Micronucleus Test (Mice)  
Dominant Lethal Test (Mice)

Long term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to two years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

**Pregnancy-Pregnancy Category C:** Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are no adequate and well controlled studies in pregnant women. CILOXAN™ Ophthalmic Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether topically applied ciprofloxacin is excreted in human milk; however, it is known that orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose. Caution should be exercised when CILOXAN™ Ophthalmic Solution is administered to a nursing mother.

**Pediatric Use:** Safety and effectiveness in children below the age of 12 have not been established. Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

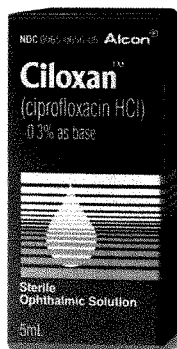
#### ADVERSE REACTIONS:

The most frequently reported drug related adverse reaction was local burning or discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients (SEE PRECAUTIONS). Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occurring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, nausea and decreased vision.

**OVERDOSAGE:** A topical overdose of CILOXAN™ Ophthalmic Solution may be flushed from the eye(s) with warm tap water.

**ANIMAL PHARMACOLOGY:** Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a one-month topical ocular study using immature Beagle dogs did not demonstrate any articular lesions.

U.S. Patent No. 4,670,444

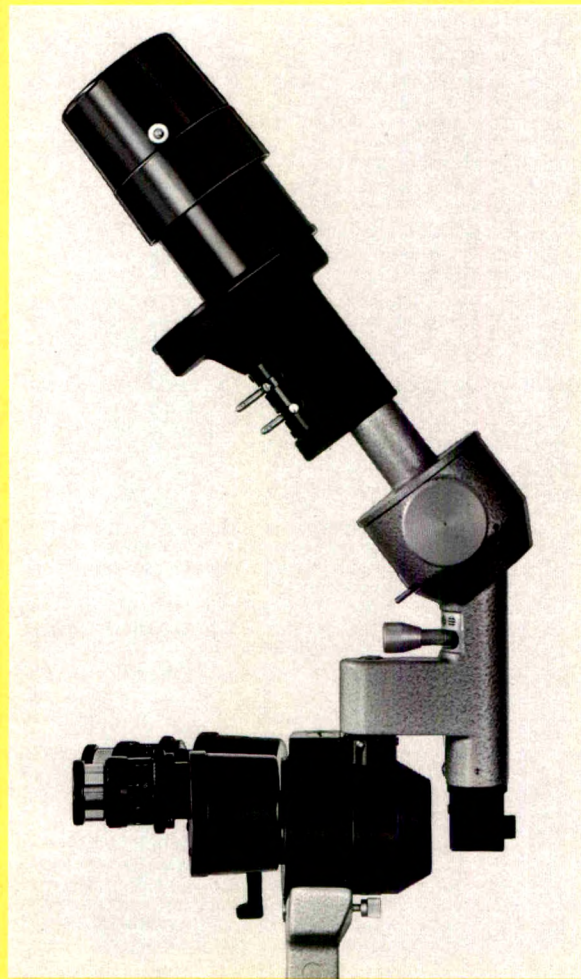


**Alcon®**  
OPHTHALMIC

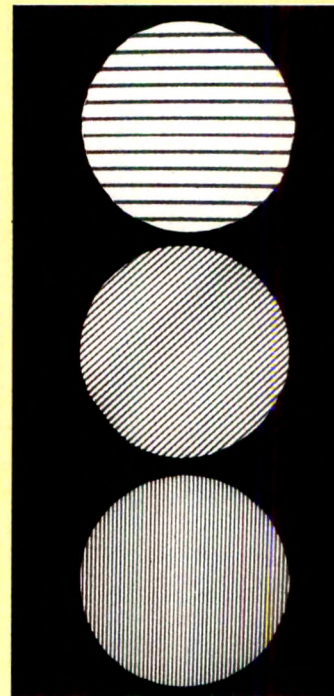
ALCON LABORATORIES, INC.  
FORT WORTH, TEXAS 76134



# Lotmar Visometer by Haag-Streit



The better way to  
predict acuity in  
cataractous and  
capsulotomy  
patients.



Comparison between the Haag-Streit interferometer and other instruments indicates that the Lotmar Visometer provides a high degree of reliability in assessing post-operative visual acuity in cataract and capsulotomy procedure. Here are some specifics.

The Lotmar Visometer easily mounted on any S Lamp 900, offers proven greater ability to penetrate denser media even with serious turbidity.

It is acknowledged to provide greater reliability in assessing postoperative

## Prospective studies in consecutive patients \*

	Predicted within	Interferometer	Potential acuity meter
<b>Capsulotomy</b> 30 patients	On line Two lines	96.0% 96.0%	33.0% 56.6%
<b>Cataract</b> 300 patients	One line Two lines	82.0% 96.0%	26.0% 64.0%

\* Wade Faulkner, M.D., F.A.C.S., Mobile Eye, Ear, Nose & Throat Center, Mobile, Alabama

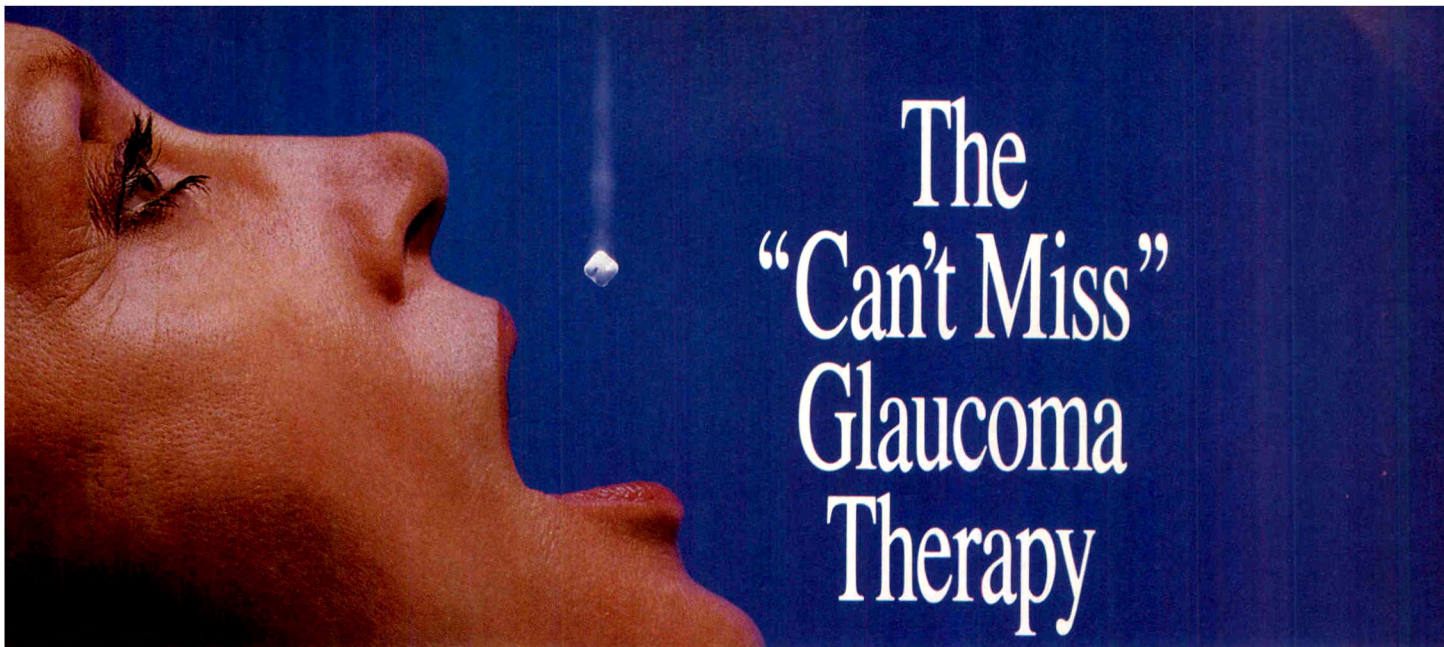
# HAAG-STREIT

**Haag-Streit Service, Inc.**

Subsidiary of Haag-Streit AG., Berne Switzerland  
7 Industrial Park, Waldwick, New Jersey 07463  
(201) 445-1110

visual acuity through its use of the moiré fringe technique as compared with letter charts. It is reasonably priced and fully supported by the leading ophthalmological instrumentation worldwide.





# The "Can't Miss" Glaucoma Therapy

## NEPTAZANE 25mg— The Dropless Way to Drop IOP

❑ Poor compliance to eyedrop regimens may significantly diminish the efficacy of glaucoma therapy<sup>1</sup> ❑ NEPTAZANE tablets have been proven effective in reducing IOP ❑ NEPTAZANE 25 mg allows for reducing and increasing doses as needed with fewer side-effects<sup>2</sup> ❑ NEPTAZANE tablets provide added control of IOP when your beta blocker,<sup>3</sup> miotic or epinephrine eyedrop does not control IOP ❑ NEPTAZANE 25 mg is oral therapy; therefore, patients may find administration and compliance easier than with eyedrops—they "can't miss" the eye with NEPTAZANE ❑ Also available as NEPTAZANE 50 mg tablets

## Neptazane<sup>®</sup> 25mg methazolamide tablets

Visit us at the AAO, Booth #210

Please see brief summary of full Prescribing Information below.

### NEPTAZANE<sup>®</sup> Methazolamide

#### Brief Summary

Before prescribing, please consult complete product information, a summary of which follows:

**INDICATIONS AND USAGE:** For adjunctive treatment of chronic simple (open-angle) glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.

**CONTRAINDICATIONS:** Severe or absolute glaucoma and chronic noncongestive angle-closure glaucoma. Of doubtful use in glaucoma due to severe peripheral anterior synechiae or hemorrhagic glaucoma. Adrenocortical, hepatic, or renal insufficiency; electrolyte imbalance state; eg, hyperchloremic acidosis; sodium and potassium depletion states.

**WARNING:** Although teratogenic effects demonstrated in rats at high doses have not been evidenced in humans, methazolamide should not be used in women of child-bearing potential or in pregnancy, especially in the first trimester, unless the expected benefits in glaucoma control outweigh potential adverse effects.

**PRECAUTIONS:** Potassium excretion is increased initially upon administration of NEPTAZANE, and in patients with cirrhosis or hepatic insufficiency, could precipitate an hepatic coma. It should be used with caution in patients on steroid therapy because of the potentiality of hypokalemic

state. Adequate and balanced electrolyte intake is essential in all patients whose concomitant clinical condition may occasion electrolyte imbalance.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, methazolamide, which may precipitate or aggravate acidosis, should be used with caution.


Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, and agranulocytosis. Precaution is advised for early detection of such reactions and the drug should be discontinued and appropriate therapy instituted.

**ADVERSE REACTIONS:** (Most are relatively mild and disappear on withdrawal or dosage adjustment): anorexia, nausea, vomiting, malaise, fatigue or drowsiness, headache, vertigo, mental confusion, depression, paresthesias of the fingers, toes, hands or feet and, occasionally, at the mucocutaneous junction of the lips, mouth, and anus. Rarely, photosensitivity has been reported. Urinary citrate excretion and uric acid output are decreased during the use of this drug, but urinary calculi have been reported only rarely. The effect on citrate excretion is less than that reported from the administration of

acetazolamide.

In order to monitor for common hematologic reactions, baseline CBC and platelet count should be obtained prior to initiating NEPTAZANE methazolamide therapy and at regular intervals during therapy. If significant changes occur, the drug should be discontinued and appropriate therapy instituted.

Rev. 2/88

Manufactured for **STORZ**<sup>™</sup>  
**STORZ OPHTHALMICS INC.**  
St. Louis, Missouri 63122  
By **LEDERLE LABORATORIES**   
A Division of American Cyanamid Company  
Pearl River, NY 10965

#### References:

1. Kass MA, Meltzer DW, Gordon M, et al. Compliance with topical pilocarpine treatment. *Am J Ophthalmol.* 1986;101:515-523.
2. Foster TS, Kiehl RA, Blouin RA, et al. Maintenance of previously controlled intraocular pressure in patients with glaucoma or ocular hypertension: comparison of four regimens of methazolamide. *Glaucoma.* 1989;11:67-71.
3. *Physicians' Desk Reference.* 43rd ed. Oradell, NJ: Medical Economics Co; 1989:594, 1395.

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# LIGHTHOUSE LOW VISION PRODUCTS LOWERS PRICES!

**Lighthouse Low Vision Products announces a significant price reduction on almost every optical product in its line.**

Since 1953, the Lighthouse has been committed to serving the needs of the low vision patient. Over the years, the Lighthouse has been the pioneer in establishing methodology for clinical services, working with suppliers in new product development, offering fully accredited continuing education courses, and carrying the broadest possible range of vision testing equipment and optical low vision devices.

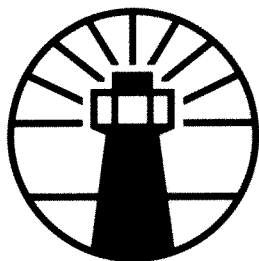
While we are generally pleased with the industry's overall progress in these areas, we are most concerned that the costs of many of the most effective low vision products are rising far too fast...and getting beyond the reach of many of the older, lower income individuals who could most benefit from such products.

**Our mission is clear: To help eyecare professionals bring the greatest number of low vision products to the greatest number of visually-impaired individuals at the lowest possible cost.**

Accordingly, we are hereby announcing significant **decreases** on just about every optical product carried in our line. It is our hope that these decreases will allow the eyecare professional to make comparable reductions in the prices that they charge their patients for these items.

We believe this new pricing policy is exactly what you would expect from the leader in low vision products and services — **The Lighthouse.**

For further information, formal quotes, a copy of our new price list, or a copy of our latest textbook quality catalog, please contact us at:



## THE LIGHTHOUSE INC.

---

**LIGHTHOUSE LOW VISION PRODUCTS**

**36-02 Northern Boulevard  
Long Island City, New York 11101  
Toll Free: (800) 453-4923  
FAX: (718) 786-0437**

**"The Most Comprehensive Resource in Vision Rehabilitation"**



# WHAT'S IN A NAME?

**Mono:** One material—PMMA.  
Proven for biocompatibility and safety.

**Flex:** MONOFLEX™ INSERTABILITY.  
User-friendly, multi-piece flexibility  
for ease of insertion.

MONOFLEX is all-PMMA, multi-piece performance defined. The "MONO" in MONOFLEX is synonymous with the biocompatibility and safety of our thermally-drawn, proven PMMA. "FLEX"—which comes from the English "flexibility"—denotes the same ease of insertability as polypropylene...with the proven benefits of all-PMMA performance.

For a more expanded definition of MONOFLEX, call Inside Sales at 1-800-TO ALCON.

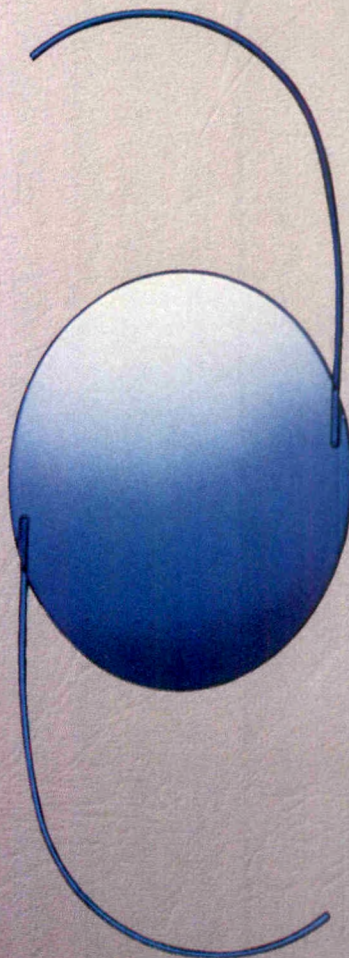
**CILCO**  
**MONOFLEX**™  
PMMA MULTI-PIECE LENSES

**MONOFLEX™ means all-PMMA,  
multi-piece performance**

**Alcon**  
SURGICAL

Innovation  
Without  
Compromise

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# Vitreous Surgery with one hand

## Compromises like this are no longer necessary with the new Xenon Illumination System from D.O.R.C.!

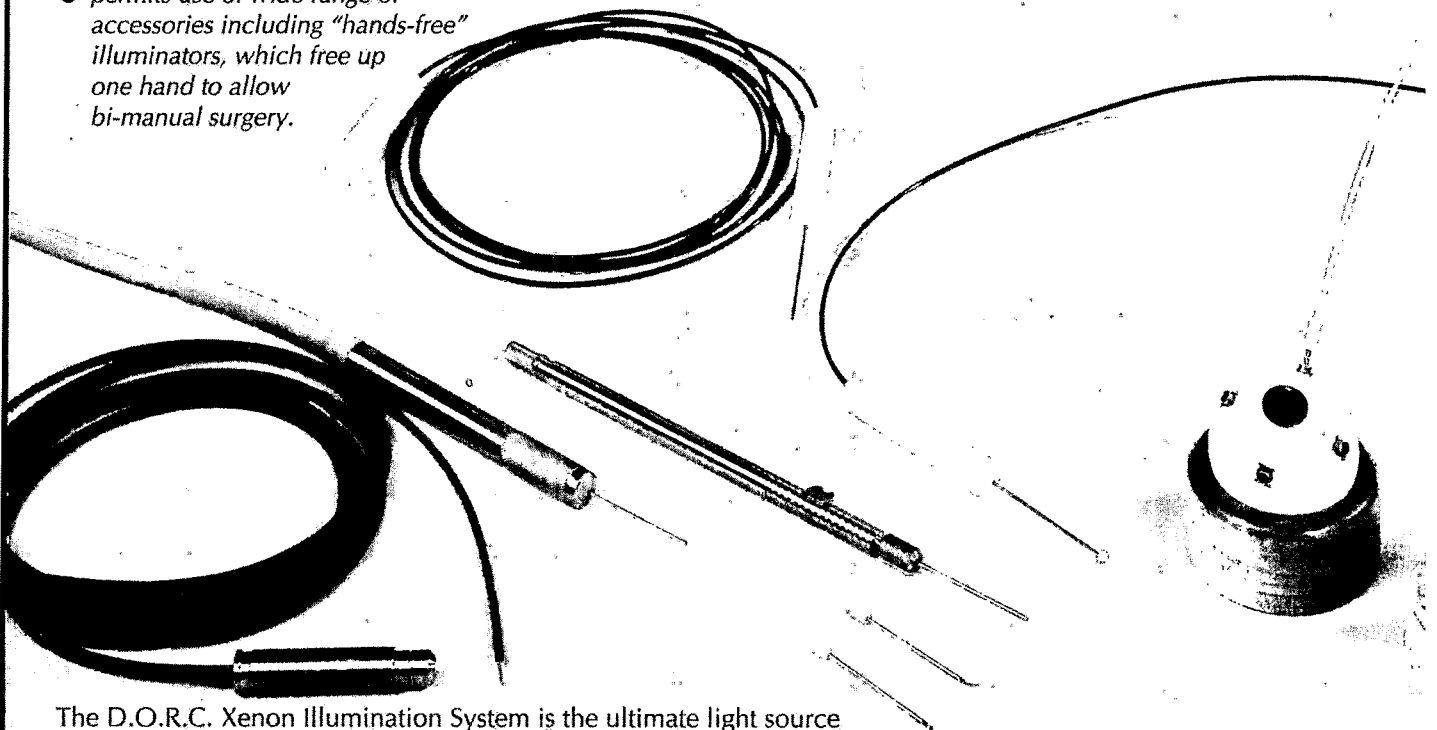
The challenge of complicated vitreous surgery is often hampered by inadequate intraocular illumination. Traditional light sources for vitreous surgery have required the surgeon to dedicate one hand to the intraocular light probe, leaving only one hand free for other instruments.

With the need to perform bi-manual vitreous surgery for the more aggressive management of vitreo-retinal disorders, this one-handed compromise is no longer acceptable...

**Nor is it required!**

**The NEW Xenon Illumination System from Dutch Ophthalmic Research Center...**

- utilizes a unique xenon light source for significantly brighter and "whiter" light
- provides ample illumination for all posterior segment procedures
- produces light intensity up to eight times brighter than halogen light sources
- permits use of wide range of accessories including "hands-free" illuminators, which free up one hand to allow bi-manual surgery.



The D.O.R.C. Xenon Illumination System is the ultimate light source for vitreous surgery. When complemented with the full array of D.O.R.C. illumination accessories, this system is unmatched in performance or value!

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**DUTCH OPHTHALMIC, USA**

10 Marshall Road, P.O. Box 968, Kingston, NH 03848

Other International:

**Medical Workshop bv**

Heresingel 28 9711 EV Groningen Holland

**DOR**  
Dutch Ophthalmic Research Center bv

**C**reeping pupillary constriction during cataract surgery—frustrating...time delaying... and possibly, dangerous. Now you can do something about this problem by using PROFENAL® ophthalmic solution—an NSAID from ALCON.®

PROFENAL solution helps maintain pupillary mydriasis throughout the entire cataract procedure, thus facilitating removal of the lens and cortical material...and enhancing implantation and positioning of the IOL.

Help prevent creeping miosis with PROFENAL...all at less than half the price of the competitive ophthalmic topical NSAIDs.\*

# TRANSCENDING THE LIMITATIONS OF CREEPING MIOSIS



**PROFENAL<sup>®</sup>**  
**(SUPROFEN) 1%**  
Sterile Ophthalmic Solution

**Alcon<sup>®</sup>**  
SURGICAL

Innovation  
Without  
Compromise

\*1991 Drug Topics Redbook

Please see next page for full prescribing information.

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BSS 022

PROFENAL solution is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis) and in individuals hypersensitive to any component of the medication. Caution should also be used when treating individuals who have previously exhibited sensitivities to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Ocularly applied nonsteroid anti-inflammatory drugs may cause increased bleeding tendency of ocular tissues in conjunction with ocular surgery. As with all other NSAIDs, PROFENAL solution should be used with caution in patients with bleeding tendencies and those taking anticoagulants. Drug Interactions—Clinical studies with acetylcholine chloride revealed no interference and there is no pharmacological basis for such an interaction. However, with other topical nonsteroidal anti-inflammatory products, acetylcholine chloride and carbachol have been ineffective when used in patients treated with these agents.



# EAGLE LABORATORIES

## "Your Instruments of Choice for Hydrodelineation, Hydrodissection and Cortical Removal"

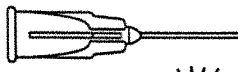
MADE IN U.S.A.

**J-HOOK NUCLEUS HYDRODISSECTOR**  
106-30 L, R, S 30 GAUGE  
LEFT, RIGHT, OR STRAIGHT HOOK  
(MAY ALSO BE USED FOR CORTICAL REMOVAL  
AT 12:00 POSITION)

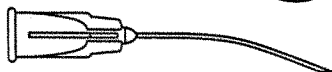


(HOOK DIMENSIONS 1.5 mm wide x 1.5 mm long)

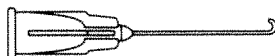
**HYDRODISSECTION CANNULAE (JOHNSON)**  
115-25 25 GA x 1"  
115-27 27 GA x 1"  
115-30 30 GA x 1"  
10 mm BEND WITH BEVELED TIP FOR EASE OF  
INSERTION THRU SMALL INCISIONS



**HYDRODELINEATION CANNULAE (JOHNSON)**  
114-25 25 GA x 1"  
114-27 27 GA x 1"  
114-30 30 GA x 1"  
WITH BEVELED TIP FOR EASE OF INSERTION THRU  
SMALL INCISION

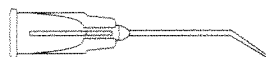


**IRRIGATING CORTEX EXTRACTOR/HYDRODISSECTOR**  
(FOR CORTICAL REMOVAL OR NUCLEUS  
HYDRODISSECTION AT THE 12:00 POSITION)  
ANGLED 20 mm LONG, STRAIGHT 23 mm LONG  
106-27 L, R, S 27 GAUGE  
LEFT, RIGHT OR STRAIGHT HOOK



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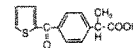
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### PROFENAL® 1% (Suprofen) Sterile Ophthalmic Solution

**DESCRIPTION:** PROFENAL® (suprofen) 1% ophthalmic solution is a topical nonsteroidal anti-inflammatory product for ophthalmic use. Suprofen chemically is  $\alpha$ -methyl-4-(2-thienylcarbonyl)benzeneacetic acid, with an empirical formula of  $C_{14}H_{12}O_3S$  and a molecular weight of 260.3. The chemical structure of suprofen is:



PROFENAL Sterile Ophthalmic Solution contains suprofen 1.0% (10 mg/mL), thimerosal 0.005% (0.05 mg/mL), caffeine 2% (20 mg/mL), edetate disodium, dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH to 7.4), and purified water. DM-00

**CLINICAL PHARMACOLOGY:** Suprofen is one of a series of phenylalkanoic acids that have shown analgesic, antipyretic, and anti-inflammatory activity in animal inflammatory diseases. Its mechanism of action is believed to be through inhibition of the cyclo-oxygenase enzyme that is essential in the biosynthesis of prostaglandins.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed on animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Prostaglandins appear to play a role in the mitotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. In clinical studies, PROFENAL has been shown to inhibit the miosis induced during the course of cataract surgery. PROFENAL could possibly interfere with the mitotic effect of intraoperatively administered acetylcholine chloride.

Results from clinical studies indicate that PROFENAL Ophthalmic Solution has no significant effect on intraocular pressure.

There are no data available on the systemic absorption of ocularly applied suprofen. The oral dose of suprofen is 200 mg every four to six hours. If PROFENAL 1% Ophthalmic Solution is applied as two drops (1 mg suprofen) to one eye five times on the day prior to surgery and three times on the day of surgery, the total applied dose over the two days would be about 25 times less than a single 200 mg oral dose.

**INDICATIONS AND USAGE:** PROFENAL Ophthalmic Solution is indicated for inhibition of intraoperative miosis.

**CONTRAINDICATIONS:** PROFENAL is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis) and in individuals hypersensitive to any component of the medication.

**WARNINGS:** The potential exists for cross sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With nonsteroidal anti-inflammatory drugs, the potential exists for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding tendency of ocular tissues in conjunction with ocular surgery.

#### PRECAUTIONS:

**General.** Use of oral suprofen has been associated with a syndrome of acute flank pain and generally reversible renal insufficiency, which may present as acute uric acid nephropathy. This syndrome occurs in approximately one in 3500 patients and has been reported with as few as one to two doses of a 200 mg capsule. If PROFENAL 1% Ophthalmic Solution is applied as two drops (1 mg suprofen) to one eye five times on the day prior to surgery and three times on the day of surgery, the total applied dose over the two days would be about 25 times less than a single 200 mg oral dose.

**Ocular.** Patients with histories of herpes simplex keratitis should be monitored closely. PROFENAL is contraindicated in patients with active herpes simplex keratitis.

The possibility of increased ocular bleeding during surgery associated with nonsteroidal anti-inflammatory drugs should be considered.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** In an 18-month study in mice, an increased incidence of hepatomas occurred in females at a dose of 40 mg/kg/day. Male mice, treated at doses of 2, 5, 10, and 40 mg/kg/day, also had an increased incidence of hepatomas when compared to control animals. No evidence of carcinogenicity was found in long term studies in doses as high as 40 mg/kg/day in the rat and mouse. Based on a battery of mutagenicity tests (Ames, micronucleus, and dominant lethal), suprofen does not appear to have mutagenic potential. Reproductive studies in rats at a dose of up to 40 mg/kg/day revealed no impairment of fertility and only slight reductions of fertility at doses of 80 mg/kg/day. However, testicular atrophy/hypoplasia was observed in a six-month dog study (at 80 mg/kg/day) and a 12-month rat study (at 40 mg/kg/day).

**Pregnancy Category C.** Reproductive studies have been performed in rabbits at doses up to 200 mg/kg/day and in rats at doses up to 80 mg/kg/day. In rats, doses of 40 mg/kg/day and above, and in rabbits, doses of 80 mg/kg/day and above, resulted in an increased incidence of fetal resorption associated with maternal toxicity. There was an increase in stillbirths and a decrease in postnatal survival in pregnant rats treated with suprofen at 2.5 mg/kg/day and above. An increased incidence of delayed parturition occurred in rats. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effect of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

**Nursing Mothers.** Suprofen is excreted in human milk after a single oral dose. Based on measurements of plasma and milk levels in women taking oral suprofen, the milk concentration is about 1% of the plasma level. Because systemic absorption may occur from topical ocular administration, a decision should be considered to discontinue nursing while receiving PROFENAL® since the safety of suprofen in human neonates has not been established.

**Pediatric Use.** Safety and effectiveness in children have not been established.

**Drug Interactions.** Clinical studies with acetylcholine chloride revealed no interference, and there is no known pharmacological basis for such an interaction. However, with other topical nonsteroidal anti-inflammatory products, there have been reports that acetylcholine chloride and carbachol have been ineffective when used in patients treated with these agents.

Interaction of PROFENAL with other topical ophthalmic medications has not been fully investigated.

#### ADVERSE REACTIONS:

**Ocular.** The most frequent adverse reactions reported are burning and stinging of short duration. Instances of discomfort, itching, and redness have been reported. Other reactions occurring in less than 0.5% of patients include allergy, irritation, pain, chemosis, photophobia, irritation, and punctate epithelial staining.

**Systemic.** Systemic reactions related to therapy were not reported in the clinical studies. It is known that some systemic absorption does occur with ocularly applied drugs, and that nonsteroidal anti-inflammatory drugs have been shown to increase bleeding time by interference with thrombocyte aggregation. It is recommended that PROFENAL be used with caution in patients with bleeding tendencies and those taking anticoagulants.

**OVERDOSAGE:** Overdosage will not ordinarily cause acute problems. If accidentally ingested, drink fluids to dilute.

**DOSAGE AND ADMINISTRATION:** On the day of surgery, instill two drops into the conjunctival sac at three, two, and one hour prior to surgery. Two drops may be instilled into the conjunctival sac every four hours, while awake, the day preceding surgery.

**HOW SUPPLIED:** Sterile ophthalmic solution, 2.5 mL in plastic DROP-TAINER® dispensers. 2.5 mL NDC 0065-0348-25

**STORAGE:** Store at room temperature.

**CAUTION:** Federal (USA) law prohibits dispensing without prescription.

US Patent Nos. 4,035,376; 4,559,343.

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342980 Revised: February 1990

Now

# #1 THERAPY FOR ROSACEA<sup>1</sup>

Un-retouched photographs from clinical studies, courtesy Arthur Sober, M.D.



Baseline



After 9 Weeks of MetroGel Therapy

## MetroGel<sup>®</sup> (metronidazole) 0.75% Topical Gel

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- Elegant gel is 95% water and contains no oils, alcohols or fragrances
- Can be used under make-up, sunscreens or moisturizers

### EXCELLENT SAFETY PROFILE

- No reports of systemic side effects
- Avoids common problems associated with oral tetracyclines such as GI distress and vaginal candidiasis

### CONVENIENT BID DOSING

- Apply a thin film of MetroGel morning and evening

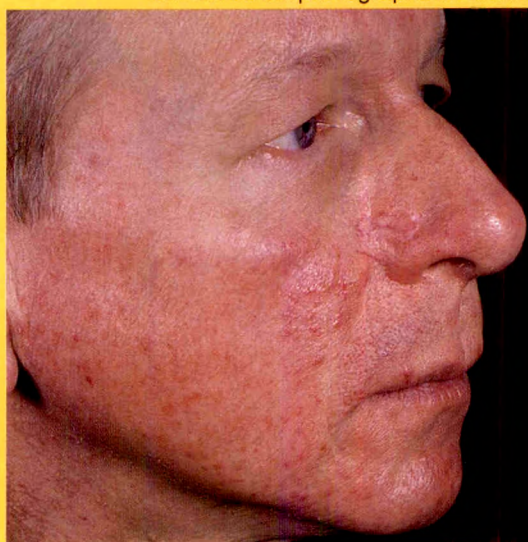
**MetroGel For Rosacea**

Curatek<sup>®</sup>

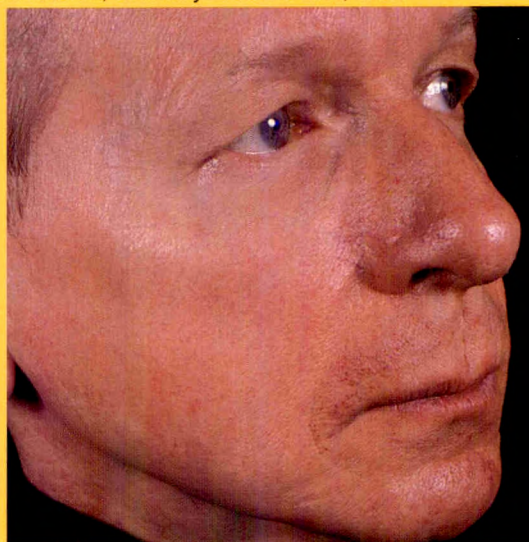


# Now #1 THERAPY FOR ROSACEA<sup>1</sup>

Un-retouched photographs from clinical studies, courtesy Arthur Sober, M.D.



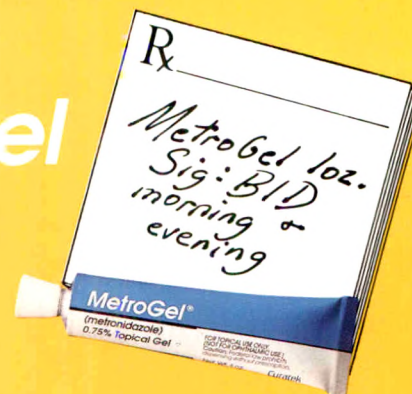
Baseline



After 9 Weeks of MetroGel Therapy

## MetroGel<sup>®</sup> (metronidazole) 0.75% Topical Gel

- Proven Effective<sup>2,3,4</sup>
- Formulated For Patient Acceptance
- Excellent Safety Profile
- Convenient BID Dosing



### Brief Summary

#### MetroGel<sup>®</sup> (metronidazole) 0.75% Topical Gel

FOR TOPICAL USE ONLY  
(NOT FOR OPHTHALMIC USE)

**CLINICAL PHARMACOLOGY** The mechanisms by which METROGEL acts in reducing inflammatory lesions of rosacea are unknown, but may include an anti-bacterial and/or an anti-inflammatory effect.

**INDICATIONS AND USAGE** METROGEL is indicated for topical application in the treatment of inflammatory papules, pustules, and erythema of rosacea.

**CONTRAINDICATIONS** METROGEL is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens, or other ingredients of the formulation.

**PRECAUTIONS** Because of the minimal absorption of metronidazole and consequently its insignificant plasma concentration after topical administration, the adverse experiences reported with the oral form of the drug have not been reported with METROGEL.

**General** METROGEL has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently, discontinue use temporarily, or discontinue use until further instructions. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia.

**Drug Interactions** Drug interactions are less likely with topical administration but should be kept in mind when METROGEL is prescribed for patients

who are receiving anticoagulant treatment. Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time.

**Carcinogenesis: Tumorigenicity in Rodents** Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. These studies have not been conducted with 0.75% metronidazole gel, which would result in significantly lower systemic blood levels than oral formulations.

**Mutagenicity Studies** Although metronidazole has shown mutagenic activity in a number of *in vitro* bacterial assay systems, studies in mammals (*in vivo*) have failed to demonstrate a potential for genetic damage.

**Pregnancy** This drug should be used during pregnancy only if clearly needed.

**Nursing Mothers** Even though METROGEL blood levels are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS** Adverse conditions reported include watery (tearing) eyes if the gel is applied too closely to this area, transient redness, and mild dryness, burning, and skin irritation. None of the side effects exceeded an incidence of 2% of patients.

**DOSAGE AND ADMINISTRATION** Apply and rub in a thin film of METROGEL twice daily, morning and evening, to entire affected areas after washing. Significant therapeutic results should be noticed within three weeks. Clinical studies have demonstrated continuing improvement through nine weeks of therapy.

Areas to be treated should be cleansed before application of METROGEL. Patients may use cosmetics after application of METROGEL.

**HOW SUPPLIED** METROGEL (0.75% metronidazole) is supplied in 1 oz. (28.4 g) aluminum tube - NDC 55326-100-21.

Caution: Federal law prohibits dispensing without a prescription.

STORE AT CONTROLLED ROOM TEMPERATURES: 59° to 86° F; 15° to 30° C.

Consult package insert for full disclosure. Package insert issued 10/8

### References:

1. Independent market research shows dermatologists prescribe MetroGel for rosacea more often than any other medication. Data on file, Curatek Pharmaceuticals, 1989.
2. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol.* 1987; 123:609-614.
3. Aronson IK, Rumsfield JA, West DP, Alexander J, Fischel JH, Paloucek FP. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm.* 1987;21:346-351.
4. Lowe NJ, Henderson T, Millikan LE, Smith S, Turk F, Parker F. Topical metronidazole for severe and recalcitrant rosacea: a prospective open trial. *Cutis.* 1989;43(3):283-286.

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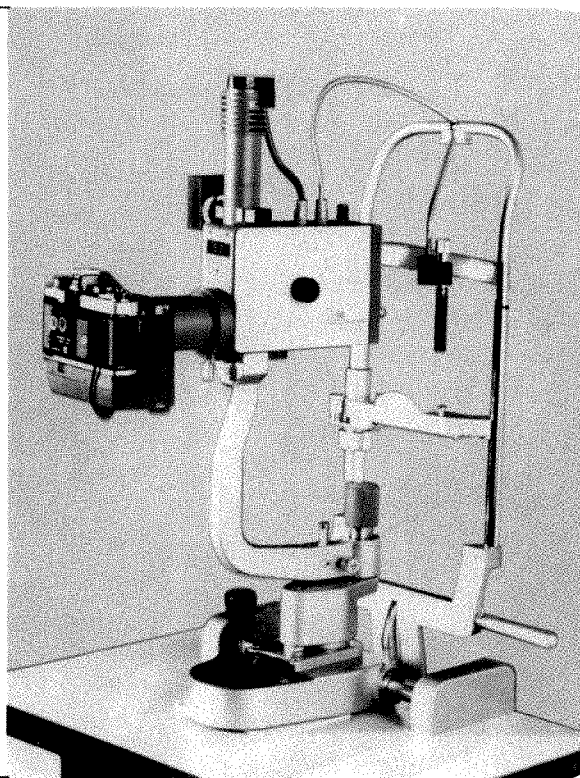
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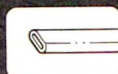
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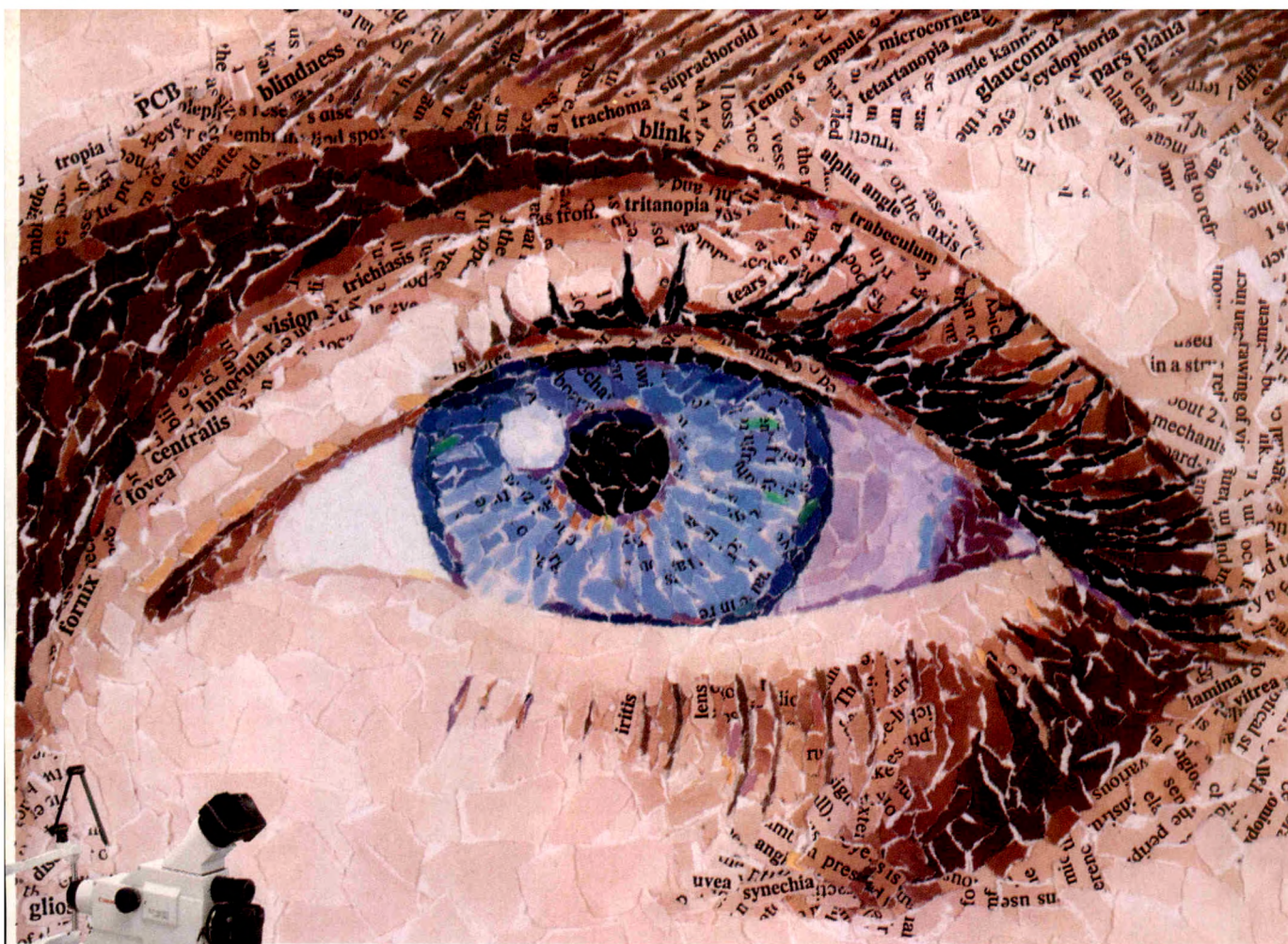
**INDICATIONS AND USAGE:** Ocufen is indicated for the inhibition of intraoperative miosis. **CONTRAINDICATIONS:** Ocufen is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis) and in individuals who are hypersensitive to any components of the medication. **WARNINGS:** With nonsteroidal anti-inflammatory drugs there exists the potential for increased bleeding due to interference with thrombocyte aggregation. There have been reports that Ocufen may cause bleeding of ocular tissue (including hyphemas) in conjunction with ocular surgery. There exists the potential for cross-sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs. **PRECAUTIONS: General:** Patients with histories of herpes simplex keratitis should be monitored closely. Ocufen is contraindicated in patients with active herpes simplex keratitis. Wound healing may be delayed with the use of Ocufen. It is recommended that Ocufen be used with caution in surgical patients with known bleeding tendencies or who are receiving other medication which may prolong bleeding time. **Drug Interactions:** In interaction of Ocufen® (flurbiprofen sodium) 0.03% Liquifilm® sterile ophthalmic solution with other topical ophthalmic medications has not been fully investigated. Although clinical studies with acetylcholine chloride and animal studies with acetylcholine chloride or carbachol revealed no interference, and there is no known pharmacological basis for an interaction, there have been reports that acetylcholine chloride and carbachol have been ineffective when used in patients treated with Ocufen. **Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies in mice and/or rats have shown no evidence of carcinogenicity or impairment of fertility with flurbiprofen. Long-term mutagenicity studies in animals have not been performed. **Pregnancy: Pregnancy category C.** Flurbiprofen has been shown to be embryocidal, delay parturition, prolong gestation, reduce weight, and/or slightly retard growth of fetuses when given to rats in daily oral doses of 0.4 mg/kg (approximately 185 times the human daily topical dose) and above. There are no adequate and well-controlled studies in pregnant women. Ocufen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from flurbiprofen sodium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** The most frequent adverse reactions reported with the use of Ocufen are transient burning and stinging upon instillation and other minor symptoms of ocular irritation. Increased bleeding tendency of ocular tissues in conjunction with ocular surgery has also been reported.



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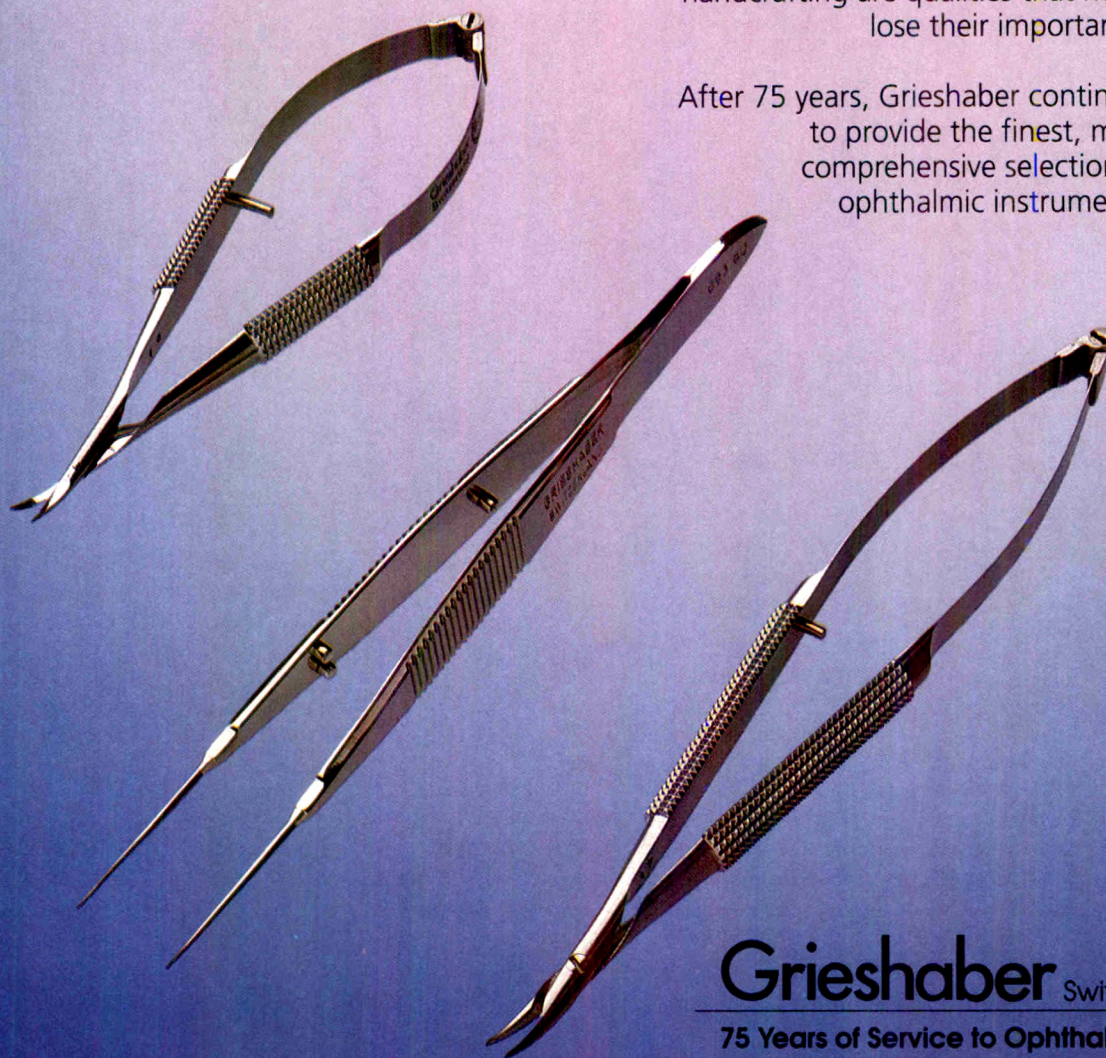


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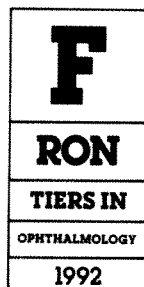
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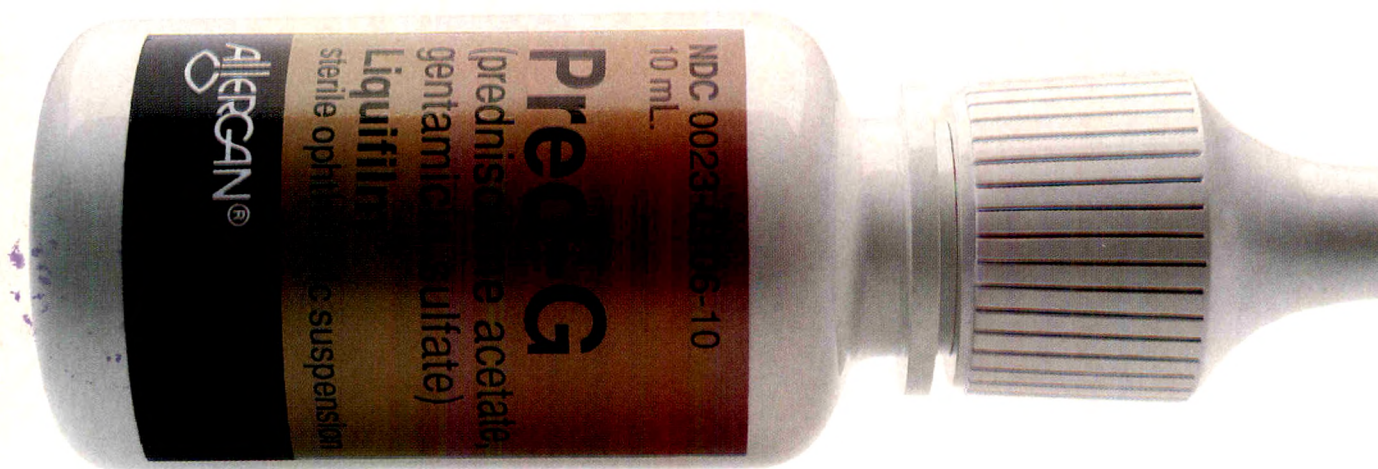
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**INDICATIONS AND USAGE:** Pred-G suspension is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies. The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye. The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: *coagulase-positive and coagulase-negative staphylococci, including Staphylococcus aureus, and certain strains that are resistant to penicillin; Group A beta-hemolytic and nonhemolytic streptococci, and Streptococcus pneumoniae; Escherichia coli; Hemophilus influenzae; Klebsiella/Enterobacter species; Neisseria species, including Neisseria gonorrhoeae; Pseudomonas aeruginosa; indole-positive and indole-negative Proteus species; and Serratia marcescens.* **CONTRAINDICATIONS:** Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of the ocular structures. Hypersensitivity to a component of the medication. (Hypersensitivity to the antibiotic component occurs at a higher rate than for other components.) Pred-G suspension is always contraindicated after uncomplicated removal of a corneal foreign body. **WARNINGS:** Prolonged use may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Employment of a steroid medication in the treatment of patients with a history of herpes simplex requires great caution. Pred-G suspension is contraindicated in patients with active herpes simplex keratitis. Pred-G Liquifilm sterile ophthalmic suspension is not for injection. It should never be injected subconjunctivally, nor should it be directly introduced into the anterior chamber of the eye. **PRECAUTIONS:** The initial prescription and renewal of the medication order beyond 20 milliliters should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. The possibility of fungal infections of the cornea should be considered after prolonged steroid dosing. **ADVERSE REACTIONS:** Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available. Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitizations. The reactions due to the steroid component in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing. Burning, stinging and other symptoms of irritation have been reported with Pred-G. Superficial punctate keratitis has been reported occasionally with onset occurring typically after several days of use. **Secondary Infection:** The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

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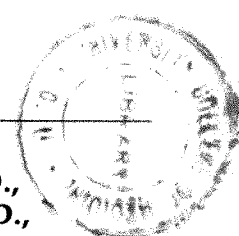
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# Repair of Retinal Detachment Caused by Cytomegalovirus Retinitis in Patients With the Acquired Immunodeficiency Syndrome

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Twenty-two eyes of 19 patients with the acquired immunodeficiency syndrome who had pars plana vitrectomy and silicone-oil injection after retinal detachment caused by cytomegalovirus retinitis were studied. All patients but one were monitored until time of death. The postoperative survival time and the factors that predicted anatomic success (retinal attachment) and functional success (visual acuity) were analyzed. No intraoperative complications were encountered. The mean survival time after surgery was four months. Of all of the preoperative and intraoperative factors studied, only the duration of cytomegalovirus retinitis was predictive of survival ( $P < .03$ ). The anatomic success rate was 89.5% (17 of 19 patients). None of the factors showed a trend or statistical significance in relation to anatomic success. Fifteen of 19 patients (79%) had lost at least two lines of Snellen visual acuity at time of death. Vision declined in a bimodal pattern (within the first postoperative month and after four months postoperatively). The optic nerve was pink and well perfused preoperatively in 16 of 19 patients (81.8%), but optic-nerve atrophy was observed postoperatively in 18 of 19 patients (95.5%). There was a trend for functional success to be influenced by increased intraocular pressure and optic-nerve atrophy,

although our sample size was too small for statistical significance.

CYTOMEGALOVIRUS RETINITIS develops in 6% to 38% of patients with the acquired immunodeficiency syndrome.<sup>1-12</sup> In most instances, it develops late in the course of AIDS,<sup>8</sup> although it may sometimes be the initial manifestation.<sup>13</sup> The use of ganciclovir is an effective treatment for cytomegalovirus retinitis, with a response rate of 80% to 100%.<sup>11,12,14-25</sup> However, up to 29% of patients may develop retinal detachment during or after treatment.<sup>26</sup> Ganciclovir may contribute to the development of retinal detachment by inhibiting scar formation.<sup>19,26</sup> However, Jabs, Enger, and Bartlett<sup>12</sup> found that a majority of their patients had retinal detachment at initial examination, before the institution of ganciclovir treatment. They also observed that all such patients had lesions extending anteriorly up to the pars plana.<sup>12</sup> Recently, studies have indicated that the development of cytomegalovirus retinitis in a patient with AIDS may not necessarily occur just before death. The median survival time has increased from six weeks to ten months in patients who respond completely to ganciclovir treatment, and is 3.1 months for those who respond partially; median survival time for patients who are unresponsive to ganciclovir treatment is one month.<sup>12</sup> This increased survival time has prompted a more aggressive approach in an attempt to preserve vision, including retinal detachment surgery. Sidikaro and associates<sup>27</sup> have suggested that pars plana vitrectomy and internal tamponade with long-acting agents such as silicone oil may be the most appropriate surgical technique.

The purpose of this study was to ascertain the

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median survival time of patients after pars plana vitrectomy and silicone-oil injection for retinal detachment caused by AIDS-associated cytomegalovirus retinitis, and to study those factors that influence anatomic and functional success after surgery in such patients. We hoped that, by monitoring all but one patient until the time of death, this study would better clarify the risks, benefits, and outcome of this surgical procedure in patients with an incurable and inevitably fatal disease.

### Patients and Methods

Twenty-two eyes of 19 patients with AIDS who underwent pars plana vitrectomy and silicone-oil injection for retinal detachment caused by cytomegalovirus retinitis were included in the study. For those three patients who had surgery on both eyes, the first procedure was used for the statistical analysis pertaining to patient survival. All patients had been examined before surgery, treated, and monitored after surgery at the Doheny Eye Institute over a two-year period. Indications for retinal detachment surgery included the following: (1) functional vision before detachment; (2) macular detachment; (3) macular-threatening cytomegalovirus retinitis, retinal detachment of the fellow eye, or both; and (4) health status adequate for surgery. All of the surgical procedures were performed by the same surgeon (P.E.L.) and consisted of a complete pars plana vitrectomy, using a standard three-port technique and silicone-oil injection with an attempt to achieve a near total fill, as described previously.<sup>28</sup> A lensectomy was not performed. Recommended precautions for patients with AIDS were heeded meticulously, including double gloving, strict isolation of all intraocular and periocular fluids, and the use of disposable instruments.<sup>29</sup>

All patients were hospitalized the night after surgery and were kept in a face-down position. They were examined six hours after surgery and before discharge the next day, and then at least once a month, with particular attention given to the Snellen visual acuity, intraocular pressure as measured by applanation tonometry, status of the retina, and optic-nerve perfusion. Optic-nerve atrophy was evaluated by serial photography as well as by clinical examinations. All but one patient was monitored until the time of death.

Survival time was estimated with the Kaplan-Meier product-limit method. The significance of predictive factors for survival was evaluated by Cox regression. For purposes of calculation, visual acuity was expressed in terms of fractions, that is,  $20/20 = 1.0$ ,  $5/200 = 0.025$ , and so forth. To investigate the relationship between changes of visual acuity and changes in intraocular pressure, the Spearman correlation technique was used. We performed Wilcoxon rank-sum tests for comparisons of two groups. A P value of  $< .05$  was considered significant.

### Results

No intraoperative complications were encountered. Most eyes had a posterior vitreous detachment and only a few inflammatory cells in the vitreous humor. All eyes had severe retinal hypoperfusion. Retinal arteriolar pulsations were observed with the infusion bottle at a minimal height, approximately 20 inches above the patient's head. Elevation of the infusion bottle caused complete arteriolar nonperfusion, as evidenced by vascular collapse. Accordingly, the infusion bottle was kept at the lowest possible height throughout the operation. Good perfusion, without any evidence of infarction, was observed in all eyes at the conclusion of surgery. Ophthalmodynamometry, which would have more dramatically illustrated this decreased perfusion pressure, was not performed.

Patient characteristics were studied (Tables 1 through 3). All patients had bilateral cytomegalovirus retinitis. All eyes showed an initial response to ganciclovir treatment and 14 of 22

TABLE 1  
PATIENT DATA OF 19 PATIENTS WITH AIDS WHO HAD  
RETINAL DETACHMENT CAUSED BY  
CYTOMEGALOVIRUS RETINITIS

	TIME*
Age	$38.3 \pm 6.3$ yrs
Duration of AIDS	$24.5 \pm 13.4$ mos
Duration of cytomegalovirus retinitis	$6.8 \pm 5.8$ mos
Duration of retinal detachment	$38.9 \pm 30.9$ days

\*Mean  $\pm$  standard deviation.

**TABLE 2**  
**RECURRENCE OF CYTOMEGALOVIRUS RETINITIS BEFORE SURGERY AND OPTIC-NERVE STATUS BEFORE AND AFTER SURGERY IN 19 PATIENTS WITH AIDS WHO HAD RETINAL DETACHMENT CAUSED BY CYTOMEGALOVIRUS RETINITIS**

RECURRENCE OF CYTOMEGALOVIRUS RETINITIS BEFORE SURGERY			OPTIC-NERVE STATUS			
NO RECURRENCE NO. (%)	ONE RECURRENCE NO. (%)	TWO RECURRENCES NO. (%)	BEFORE SURGERY		AFTER SURGERY	
			NORMAL NO. (%)	ATROPHIC NO. (%)	NORMAL NO. (%)	ATROPHIC NO. (%)
12 (63.2)	5 (26.3)	2 (10.5)	15 (78.9)	4 (21.1)	1 (5.3)	18 (94.7)

eyes (63.6%) showed no recurrence at maintenance treatment. No patient had a postoperative recurrence of cytomegalovirus retinitis.

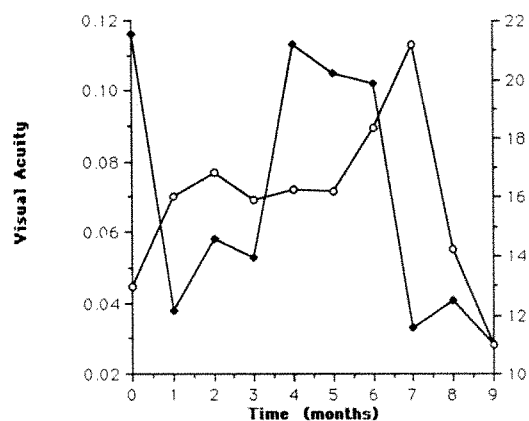
Fifteen of 19 patients (79%) had lost at least two lines of Snellen visual acuity at time of last follow-up. Visual acuity was found to decrease in a bimodal pattern. Twelve of 19 patients (63%) had a decrease in vision within one month. Three of seven eyes (43%) showed a gradual decline four months after surgery in the patients who survived. Intraocular pressure increase paralleled this bimodal pattern (Fig. 1). The intraocular pressure was increased by at least 4 mm Hg in eight of the 12 eyes (66.7%) that suffered visual loss within one month. One of the three eyes (33.3%) that had visual decline after four months showed an increased intraocular pressure. Visual acuity declined ( $-0.2 \pm 0.1$ ) and intraocular pressure increased ( $+3.4 \pm 1.2$ ) in 14 eyes in which the optic nerve appeared clinically normal before surgery but which appeared atrophic two to four months after surgery. However, slight visual acuity improvement ( $+0.004 \pm 0.01$ ) and intraocular pressure decline ( $-0.5 \pm 0.2$ ) developed in four eyes that had optic-nerve atrophy both before and after surgery (Fig. 2). Because of the small

sample size, these trends were not statistically significant ( $P = .12$  and  $P = .10$ , respectively). Only one of 15 eyes (6.7%) with a clinically normal optic nerve before surgery retained a well-perfused, pink optic nerve at time of death. The optic nerve was pink and well perfused before surgery in 18 of 22 eyes (81.8%), but optic-nerve atrophy was observed after surgery in 21 of 22 eyes (95.5%). Retinal reattachment was achieved in all patients, and 17 of 19 patients (89.5%) continued to have reattachment at the time of death, despite epiretinal membrane formation or proliferative vitreoretinopathy (C1 to D2) in 21 of 22 eyes (95.5%).

The relationship of the variables listed in Tables 1 through 3 to survival time, anatomic success as defined by retinal attachment, and functional success as defined by visual acuity

**TABLE 3**  
**QUADRANTS INVOLVED IN 19 PATIENTS WITH AIDS WHO HAD RETINAL DETACHMENT CAUSED BY CYTOMEGALOVIRUS RETINITIS**

QUADRANTS INVOLVED	CYTOMEGALOVIRUS RETINITIS NO. (%)	ATROPHIC HOLE NO. (%)	RETINAL DETACHMENT NO. (%)
1	2 (10.5)	4 (21.1)	3 (16.8)
2	9 (47.4)	12 (63.2)	9 (47.4)
3	5 (26.3)	2 (10.5)	2 (10.5)
4	3 (15.8)	1 (5.3)	5 (26.3)



**Fig. 1** (Dugel and associates). Visual acuity and intraocular pressure changes after surgery. Mean visual acuity declined in a bimodal pattern, one month before and four months after surgery. Mean intraocular pressure increases tended to precede the visual loss. Visual acuity is expressed in fractions (that is,  $20/20 = 1.0$ ,  $5/200 = 0.025$ , and so forth). Diamonds indicate visual acuity and circles indicate intraocular pressure.



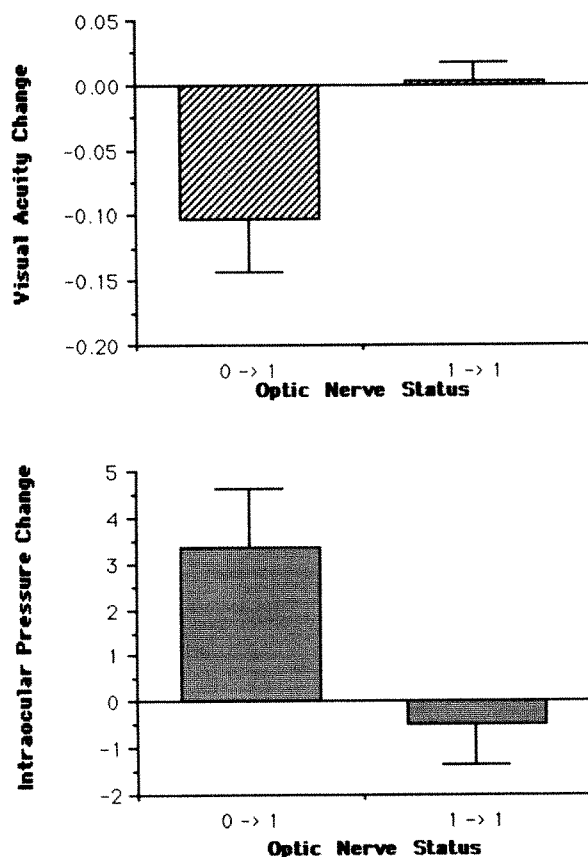


Fig. 2 (Dugel and associates). Relationships of visual acuity and intraocular pressure and optic-nerve pallor. Eyes with normal preoperative and pale postoperative optic nerves had worse vision (left) and higher intraocular pressures (right) than those with pale preoperative and postoperative optic nerves. Visual acuity change is expressed as the difference in immediately preoperative and final postoperative visual acuity expressed in fractions. Intraocular pressure change is expressed as the difference in immediately preoperative and final postoperative intraocular pressure measurement. A positive sign denotes an increase and a negative sign denotes a decrease. 0 equals pink healthy optic nerve, 1 equals pale optic nerve, and arrow equals preoperative to postoperative.

was studied. The median survival time after surgery was four months (Fig. 3). Of the factors studied, only the duration of cytomegalovirus retinitis proved significant ( $P = .03$ ) to survival. None of the factors showed a trend or statistical significance in relation to anatomic success. However, visual acuity was convincingly influenced by intraocular pressure and optic-nerve atrophy (Fig. 2), although our sample was too small to confirm statistical significance.

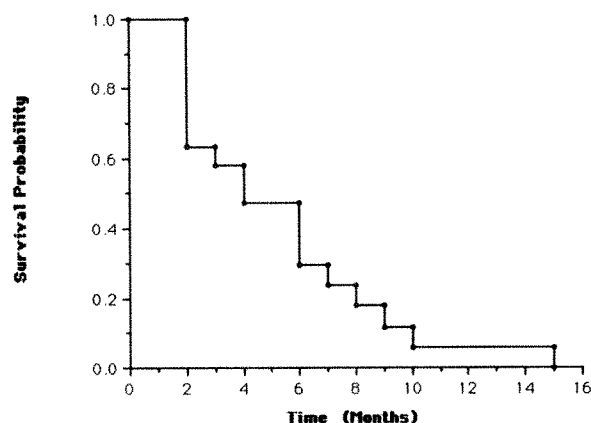


Fig. 3 (Dugel and associates). Kaplan-Meier survival probability curve after surgery. Median postoperative survival time was four months.

## Discussion

In our study, the median survival time after pars plana vitrectomy and silicone-oil injection was four months. Only one of 22 patients (5%) remained alive one year after surgery. All but one patient was monitored until death. Our results suggested that the median survival time after surgery is less than that for patients who respond completely to ganciclovir treatment, but greater than that for those who have a partial response or who are unresponsive.<sup>12</sup> All of our patients did respond initially to ganciclovir treatment, and this may have caused their retinal detachment by inhibiting scar formation.<sup>19,26</sup> Only the duration of cytomegalovirus retinitis, which may reflect immunologic status,<sup>12</sup> was predictive of survival.

Anatomic reattachment with silicone oil occurred in 17 of 19 (89.5%) of our patients. However, the functional success was poor. Sidikaro and associates<sup>27</sup> found similar results in their study of three eyes with retinal detachment caused by cytomegalovirus retinitis that underwent pars plana vitrectomy and silicone-oil injection. In our study, only four of 19 patients (21%) had better vision at the time of death than they had before surgery, and only eight (42%) had vision of 5/200 or better at the time of death. The bimodal pattern of visual loss suggests that an intraoperative or immediately postoperative injury may have caused the early postoperative visual loss, whereas a continued postoperative injury may have caused the later, more gradual, loss of vision. Only

intraocular pressure and optic-nerve atrophy were found to predict visual outcome (Figs. 1 and 2).

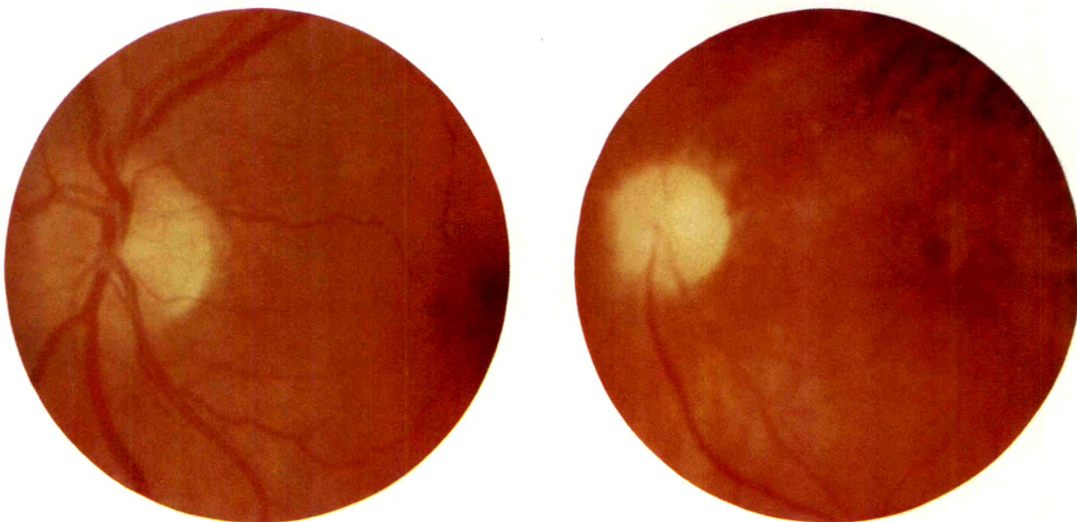
Intraocular pressure increases are known to be common immediately after pars plana vitrectomy and silicone-oil injection.<sup>30</sup> In a study of 48 patients without AIDS undergoing pars plana vitrectomy and silicone-oil injection, a postoperative intraocular pressure increase of 10 mm Hg was found in 27 of 48 patients (56%) (range, 10 to 53 mm Hg; mean increase, 21.6 mm Hg).<sup>30</sup> The intraocular pressure increases were detected at between six hours and 60 days after surgery, with 93% showing an increase by the second postoperative day.<sup>30</sup> Many other studies have found long-term and short-term intraocular pressure increases after intravitreal silicone-oil injection.<sup>28,31-37</sup> In our study, increased intraocular pressure paralleled the bimodal pattern of visual acuity loss (Fig. 1).

We observed that the retinal vascular perfusion pressure in all eyes was low during surgery, as evidenced by arteriolar pulsations with a low infusion pressure. Pepose and associates<sup>9</sup> documented retinal microvascular abnormalities, microaneurysms, and ischemic maculopathy in patients with AIDS; their ultrastructural studies showed occluded vessel lumens, swollen endothelial cells, thickened basal laminae, and degenerating pericytes.<sup>9</sup> We believe, therefore, that the early visual loss may be caused by intraoperative or immediate postoperative intraocular pressure increases (Fig. 4) and that

the gradual loss in vision may be caused by increased intraocular pressure, both causing ischemia in an eye already compromised by microvasculopathy (Fig. 5). This ischemia was evidenced by the development of optic-nerve atrophy in 21 of 22 eyes (95.5%).

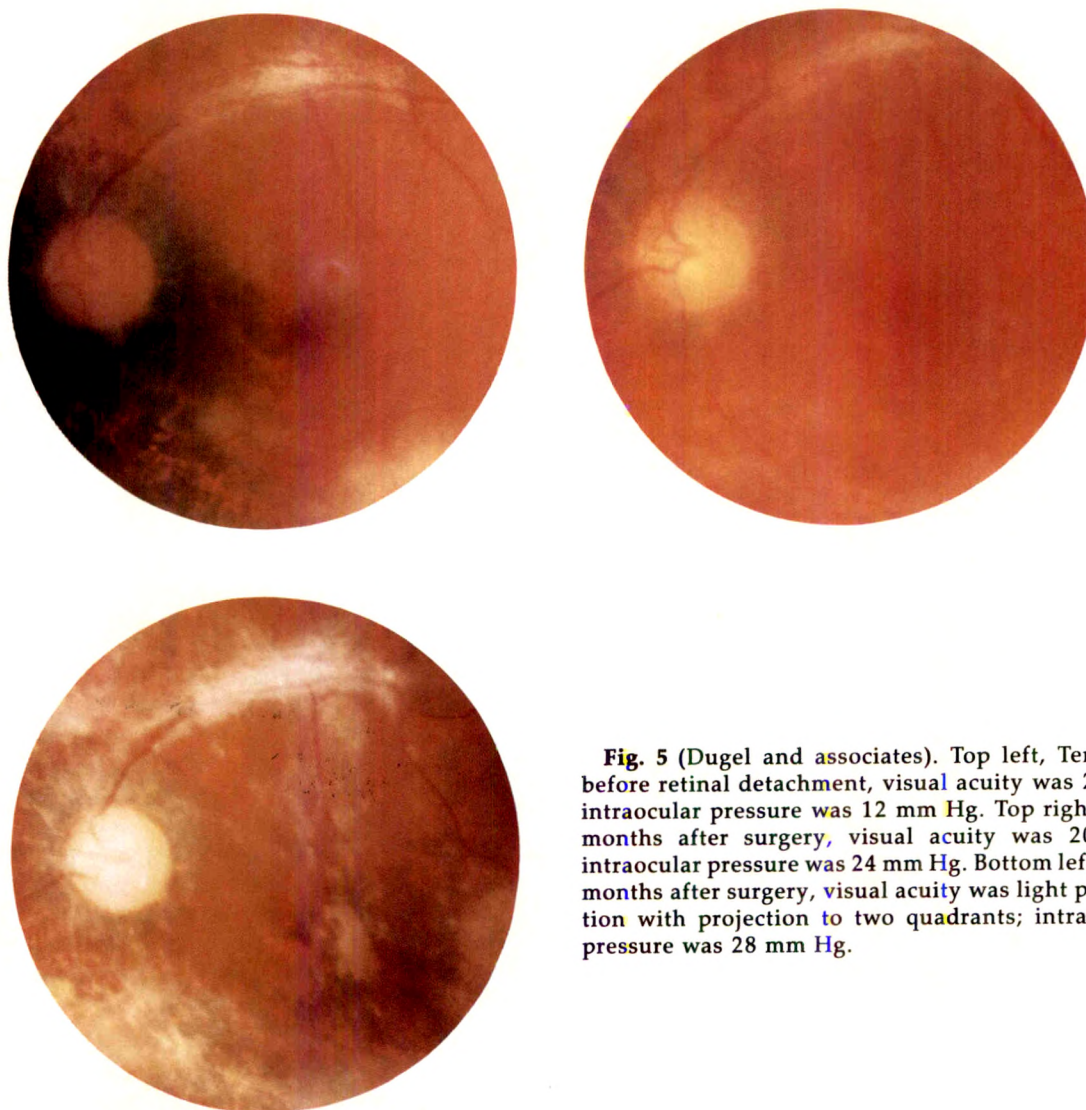
The possibility of optic-nerve atrophy developing from cytomegalovirus papillitis or silicone-oil toxicity must be considered. Patients with cytomegalovirus papillitis usually do develop peripapillary retinitis.<sup>38</sup> However, none of our patients demonstrated postoperative recurrence of any cytomegalovirus retinitis. Early experimental evidence of silicone-oil retinal toxicity<sup>39-41</sup> has been disputed by numerous investigators.<sup>42-49</sup> However, Chan and Okun<sup>50</sup> have recently suggested that direct contact between silicone oil and the human retina over a period of many years may cause a loss of retinal function. Optic-nerve atrophy was evident within six months after surgery in most of our patients. It is unlikely, therefore, that optic-nerve atrophy was caused by cytomegalovirus papillitis or silicone-oil toxicity in this study.

Our study suffers from the handicaps inherent in any small, uncontrolled study conducted in a referral center. However, despite these shortcomings, we believe that several important findings have resulted from this study. First, median patient survival time after pars plana vitrectomy with silicone-oil injection is four months. Second, although postoperative anatomic success is excellent, functional suc-



**Fig. 4** (Dugel and associates). Ten days before retinal detachment, visual acuity was 20/40; intraocular pressure was 9 mm Hg (left). One month after surgery, visual acuity was light perception with projection to one quadrant; intraocular pressure was 22 mm Hg (right).





**Fig. 5** (Dugel and associates). Top left, Ten days before retinal detachment, visual acuity was 20/50; intraocular pressure was 12 mm Hg. Top right, Two months after surgery, visual acuity was 20/100; intraocular pressure was 24 mm Hg. Bottom left, Four months after surgery, visual acuity was light perception with projection to two quadrants; intraocular pressure was 28 mm Hg.

cess is poor. Third, visual loss may develop rapidly within the first postoperative month or more gradually over several months. Fourth, vision in almost all patients is limited by optic-nerve atrophy secondary to ischemia. Fifth, strict control of intraocular pressure throughout and after surgery may be an important factor in preventing retinal ischemia and optic-nerve atrophy, and therefore determine visual success. The effects of prolonging or restoring low vision (especially in patients with bilateral retinal detachments) on self-sufficiency or emotional well-being were not analyzed. The patient's satisfaction in knowing that all that can be done to preserve vision is being done must be weighed against the emotional and physical trauma of major surgery that seems to have a poor outcome. A frank discussion of visual prognosis in the context of life expectan-

cy and the status of the fellow eye is important in the preoperative care of the patient. The United States government will spend approximately \$1.9 billion on AIDS research and treatment in 1992. We believe that a study to evaluate the health and financial implications of operating on patients with retinal detachment secondary to cytomegalovirus retinitis is warranted.

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# Cytomegalovirus Retinopathy as the Initial Manifestation of the Acquired Immunodeficiency Syndrome

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Of 100 consecutive patients with human immunodeficiency virus infection and cytomegalovirus retinopathy, 15 did not have a previous diagnosis of the acquired immunodeficiency syndrome before the ocular infection. All had other HIV-related disorders that would place them in Group IV of the Centers for Disease Control hierarchical classification system for HIV infections. In nine patients, cytomegalovirus retinopathy was the only disorder that fulfilled the Centers for Disease Control criteria for diagnosis of AIDS. In the other six, examination disclosed additional preexistent or concurrent nonocular disorders that were also diagnostic of AIDS. No demographic, medical, or ophthalmic characteristics distinguished the nine patients for whom cytomegalovirus retinopathy was initially the only manifestation of AIDS. On the basis of published figures for the prevalence of cytomegalovirus retinopathy in patients with AIDS, and the incidence with which HIV-infected persons develop AIDS, it is estimated that approximately 1.8% of patients with AIDS have cytomegalovirus retinopathy as the first manifestation and that less than 1% of HIV-infected persons will develop cytomegalovirus retinopathy as the initial manifestation of AIDS during the first seven years after infection with HIV.

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CYTOMEGALOVIRUS RETINOPATHY is usually a late manifestation of the acquired immunodeficiency syndrome, presumably because it develops in patients with the most severe degrees of immunosuppression.<sup>1,2</sup> Nevertheless, this opportunistic infection is an indicator disease that fulfills Centers for Disease Control criteria for the diagnosis of AIDS,<sup>3,4</sup> and has been reported to be the first manifestation of the syndrome in some patients.<sup>5-10</sup> In a previously published study,<sup>10</sup> we found that 15 of 100 patients with cytomegalovirus retinopathy and HIV infection did not have a diagnosis of AIDS when the ocular infection was discovered. Furthermore, it was found that these patients may have a poorer prognosis for survival than other patients at the time of AIDS diagnosis.

Because of the possible prognostic relevance of cytomegalovirus retinopathy when it is the index diagnosis (first indicator disease) for AIDS, additional information regarding this subset of patients was sought. Demographic, medical, and ophthalmic disease factors were investigated further to characterize more accurately the subset of patients from our previous study for whom cytomegalovirus retinopathy was the index diagnosis. Such information might help to identify patients at greatest risk for early cytomegalovirus retinopathy, thus facilitating appropriate early treatment to preserve vision. Also, the frequency with which HIV-infected individuals will develop cytomegalovirus retinopathy as the first manifestation of AIDS is estimated.

## Material and Methods

Fifteen patients with cytomegalovirus retinopathy who did not have a previous diagnosis of AIDS were studied. They were selected from a larger series of 100 consecutive patients with HIV infection and cytomegalovirus retinopathy examined at the Jules Stein Eye Institute be-



tween 1981 and 1988.<sup>10</sup> Serologic evidence of HIV infection was confirmed for these 15 patients. For the remaining 85 patients in the total population, confirmation that the diagnosis of AIDS was made on the basis of Centers for Disease Control criteria other than cytomegalovirus retinopathy was obtained by review of medical records or discussion, or both, with the patients' primary-care physicians.

The 15 patients without a previous diagnosis of AIDS were studied further by review of hospital records and in some cases by discussion with their primary-care physicians. Clinical signs and symptoms attributable to HIV infection were identified, and evidence of other preexistent or concurrent disorders included in the Centers for Disease Control surveillance definition of AIDS was sought. Patients were assigned to a group within the hierarchical Centers for Disease Control classification system for HIV infections.<sup>4</sup> The duration of all HIV-related disorders was determined whenever possible for these 15 patients. Patient age and ophthalmic characteristics (extent and location of disease) were available from the previous study of these patients.<sup>10</sup>

## Results

All 15 patients were infected with HIV before development of cytomegalovirus retinopathy, although none had a diagnosis of AIDS. In no cases did cytomegalovirus retinopathy develop in completely asymptomatic individuals.

In six of the 15 patients, preexisting or concurrent diseases (not including concurrent, nonocular cytomegalovirus infection) that are included in the Centers for Disease Control surveillance definition of AIDS, but that had not been identified or diagnosed correctly before the development of cytomegalovirus retinopathy were evident. Two patients had Kaposi sarcoma; one patient had both Kaposi sarcoma and presumptive *Pneumocystis carinii* pneumonia; one patient had cutaneous herpes simplex virus lesions of more than five weeks' duration; one patient had intracerebral toxoplasmosis; and one patient had invasive esophageal candidiasis. The time interval between the onset of these conditions and the diagnosis of cytomegalovirus retinopathy (that is, the discrepancy between the earliest potential date and the actual date of AIDS diagnosis) ranged from one to ten months (median, 7.5 months) in four patients and was not known in two patients. In addition, to these indicator diseases, five of the

six patients also had other HIV-related disorders, including lymphadenopathy in one, constitutional symptoms in three, and oral candidiasis in three (Table).

In nine of 100 patients (9%), cytomegalovirus retinopathy appeared to be the first and the only clinically apparent disease to be present that is included in the Centers for Disease Control surveillance definition of AIDS. Among these nine patients, eight had a history of constitutional symptoms. The date of onset was unknown in two patients; the remaining six had symptoms for one to 24 months (median, 12 months). Of these eight patients, five also had oral candidiasis. Furthermore, two of these five patients also had persistent lymphadenopathy. In the ninth patient, the only recorded manifestation of HIV infection was severe persistent night sweats with onset ten months before diagnosis of cytomegalovirus retinopathy.

One of these nine patients may actually have had an indicator disease for AIDS other than cytomegalovirus retinopathy. He had clinical signs of HIV encephalopathy, but adequate examination to confirm diagnosis of this condition had not been performed. He was, therefore, classified in this report as a patient in whom cytomegalovirus was the only disease diagnostic of AIDS.

The Centers for Disease Control classification system for HIV infections places patients into four groups.<sup>4</sup> It is a hierarchical system that only permits forward reclassification; reassignment into a lower classification is not allowed even if there is regression of a patient's clinical signs and symptoms. Group I includes patients with transient clinical signs and symptoms that can develop shortly after HIV infection. Group II includes HIV-infected patients with no clinical signs or symptoms of disease. Group III includes patients with only persistent generalized lymphadenopathy. Group IV includes patients with fever, weight loss, diarrhea, and other nonspecific constitutional clinical signs of disease (Subgroup A), neurologic disease (Subgroup B), secondary infectious diseases (Subgroup C), secondary neoplasms (Subgroup D), and other conditions (Subgroup E). These subgroups are not mutually exclusive. Patients in Groups III and Subgroup IV-A have previously been referred to by a variety of terms, including AIDS-related complex. Subgroup IV-C is further divided into two categories. Category C1 contains patients with one or more of the following 12 specified diseases listed in the Centers for Disease Control surveillance definition of AIDS: *Pneumocystis carinii* pneumonia; cryp-

**TABLE**  
**PATIENTS WITH CYTOMEGALOVIRUS RETINOPATHY AS INITIAL MANIFESTATION OF AIDS**

PATIENT, AGE (YRS)	HIV-ASSOCIATED ILLNESSES NOT DIAGNOSTIC OF AIDS		DISEASES DIAGNOSTIC OF AIDS IN ADDITION TO CYTOMEGALOVIRUS RETINOPATHY AT TIME OF DIAGNOSIS		PATIENT CLASSIFICATION	
	DISORDER	MONTHS BEFORE DIAGNOSIS OF CYTOMEGALOVIRUS RETINOPATHY	DISEASE	MONTHS BEFORE DIAGNOSIS OF CYTOMEGALOVIRUS RETINOPATHY	GROUP	SUBGROUP (CATEGORY)
1, 28	Lymphadenopathy; cotton-wool spots	7 7	Kaposi sarcoma	Unknown	IV	D
2, 38	Oral candidiasis	7	Chronic cutaneous herpes simplex virus lesions	7	IV	C (C-1, C-2)
3, 54	Constitutional symptoms <sup>†</sup> ; oral candidiasis	12 Unknown	None	—	IV	A, C (C-2)
4, 37	Constitutional symptoms	1	None	—	IV	A
5, 31	Constitutional symptoms; oral candidiasis	Unknown	Presumptive <i>P. carinii</i> pneumonia; Kaposi sarcoma	8 Unknown	IV	A, C, D (C-1, C-2)
6, 38	Constitutional symptoms; oral candidiasis	24 Unknown	None	—	IV	A, C (C-2)
7, 40	Lymphadenopathy; constitutional symptoms; oral candidiasis	7 7 2	None	—	IV	A, C (C-2)
8, 27	Constitutional symptoms	12	None	—	IV	A
9, 39	Constitutional symptoms; oral candidiasis	18 18	None	—	IV	A, C (C-2)
10, 37	Constitutional symptoms	Unknown	None	—	IV	A
11, 45	Constitutional symptoms; oral candidiasis	10 10	Esophageal candidiasis	10	IV	A, C (C-1, C-2)
12, 40	None documented	—	Kaposi sarcoma	1	IV	D
13, 24	Constitutional symptoms	Unknown	Intracerebral toxoplasmosis	Unknown	IV	A, C (C-1)
14, 45	Fatigue; night sweating <sup>‡</sup>	10	None	—	IV	E
15, 25	Lymphadenopathy; constitutional symptoms; oral candidiasis	Unknown Unknown Unknown	None	—	IV	A, C (C-2)

\*Centers for Disease Control classification system for patients with HIV infection.<sup>4</sup> Patients have been assigned on the basis of all diseases other than cytomegalovirus retinopathy, corresponding to the classification into which the patient would have been assigned immediately before development of cytomegalovirus retinopathy, with the assumption that all coexistent diseases had their onset before cytomegalovirus retinopathy. (According to Centers for Disease Control criteria, all patients with cytomegalovirus retinopathy are classified as Group IV, Subgroup C, Category C-1.)

<sup>†</sup>Constitutional symptoms fulfilling criteria for Group IV, Subgroup A include fever persisting more than one month; involuntary weight loss of greater than 10% of baseline value; or diarrhea persisting more than one month, in the absence of a concurrent illness or condition other than HIV infection that would explain the findings.

<sup>‡</sup>This patient had a history of slowed mentation described as dementia; evaluation was not adequate to confirm a diagnosis of HIV encephalopathy (Group IV, Subgroup B), which is diagnostic of AIDS.

<sup>§</sup>Symptoms not meeting the criteria for Group IV, Subgroup A fall into Group IV, Subgroup E.



tosporidiosis with diarrhea persisting longer than one month; toxoplasmosis of the brain affecting a patient older than 1 month; extraintestinal strongyloidiasis; isosporiasis with diarrhea persisting for longer than one month; candidiasis of the esophagus, tracheae, bronchi, or lungs; extrapulmonary cryptococcosis; disseminated histoplasmosis (at a site other than or in addition to lungs or cervical or hilar lymph nodes); *Mycobacterium avium* complex or *M. kansasii* infection; cytomegalovirus disease of an organ other than liver, spleen, or lymph nodes in a patient older than 1 month; herpes simplex virus infection causing a mucocutaneous ulcer that persists longer than one month, or bronchitis, pneumonitis, or esophagitis for any duration affecting a patient older than 1 month; and progressive multifocal leukoencephalopathy. Category C2 contains patients with other specified secondary infectious diseases, including oral candidiasis.

All patients in this study can be included in Group IV, Subgroup C, Category C1 because of their cytomegalovirus retinopathy. For instructional purposes, however, the categories identified in the Table for each patient are determined on the basis of all diseases other than cytomegalovirus retinopathy, corresponding to the classification in which the patient would have been included immediately before development of cytomegalovirus retinopathy, with the assumption that all other concurrent diseases developed before cytomegalovirus retinopathy. No patients could be classified into Group I, II, or III.

A comparison of the nine patients for whom cytomegalovirus retinopathy was the only indicator disease for AIDS with the other six patients in this study and with the other 85 patients in the total population from which they were selected disclosed no differences in patient gender, age, year of cytomegalovirus retinopathy diagnosis, extent of retinopathy at diagnosis, or location of retinopathy in the fundus (data not shown).

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## Discussion

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Cytomegalovirus retinopathy, the most common ocular opportunistic infection in patients with AIDS, is usually a late manifestation of the syndrome. Henderly and associates<sup>5</sup> studied eight patients in whom cytomegalovirus retinopathy was the first clinically apparent manifestation of AIDS, but the total population from

which these patients were drawn was not stated, leaving the magnitude of this problem unknown. Subsequent studies<sup>6,7,9,10</sup> have shown that 7% to 15% of patients with cytomegalovirus retinopathy do not have a diagnosis of AIDS at the time the ocular disease is identified, but the frequency with which cytomegalovirus retinopathy develops in the total population of HIV-infected patients is not known, and the studies do not identify whether these patients have unique characteristics.

The acquired immunodeficiency syndrome is the most severe in a spectrum of disorders caused by HIV infection. Persons infected with HIV may be asymptomatic or they may develop disorders such as fever, weight loss, fatigue, or non-life-threatening infections that do not meet the Centers for Disease Control surveillance definition for AIDS. The Centers for Disease Control have developed a classification system for all HIV-related disorders.<sup>4</sup> It is a hierarchical system comprising four groups, with each successive group representing a more advanced stage of disease. Patients whose clinical course fulfills the surveillance definition of AIDS fall into Group IV, Subgroups B, C (Category C1), or D. Among the specified infectious diseases in Subgroup IV-C1 is disseminated cytomegalovirus infection; cytomegalovirus retinopathy is an accepted clinical sign of disseminated disease in these patients and therefore can be an index disease, establishing the diagnosis of AIDS in the absence of any other criteria.

Other retinal diseases, including the microvasculopathy that causes cotton-wool spots and retinal infections with *Toxoplasma gondii* and varicella-zoster virus, have developed in HIV-infected individuals without other clinical signs of serious disease.<sup>11-13</sup> They are not, however, indicator diseases and, therefore, cannot be the initial manifestation of AIDS.

All patients in this study would have been included in Group IV even if they had not developed cytomegalovirus retinopathy. It is therefore unlikely that cytomegalovirus retinopathy will be found in patients with asymptomatic or minimally symptomatic HIV disease.

It is estimated that one million individuals in the United States are infected with HIV.<sup>14</sup> In a San Francisco study,<sup>15</sup> HIV infection had progressed to AIDS in 25% of individuals within seven years of seroconversion, a figure similar to estimates made by other investigators. The reported prevalence of cytomegalovirus retinopathy among AIDS patients has ranged from 6% to 34%.<sup>1,2,6,16-18</sup> For this study, we used the

generally accepted estimate that cytomegalovirus retinopathy develops in at least 20% of patients with AIDS. This study shows that 9% of patients with cytomegalovirus retinopathy will have this infection as the only manifestation of the syndrome at diagnosis, a figure comparable to the 7% to 11% frequency reported by other investigators.<sup>6,7,9</sup> On the basis of these figures, approximately 1.8% of patients with AIDS will therefore have cytomegalovirus retinopathy as the first manifestation of the syndrome. Jabs, Enger, and Bartlett<sup>9</sup> found the frequency to be approximately 3%. Recent Centers for Disease Control statistics state that cytomegalovirus retinopathy is reported to them as the index diagnosis for AIDS in 0.45% of cases (Harold Van Patten, Deputy Chief, Surveillance Branch, Division of HIV/AIDS, Centers for Disease Control, written communication, July 1990).

The theorem of total probabilities can be used to estimate the number of persons from the total HIV-infected population who will develop cytomegalovirus retinopathy during a seven-year period. The theorem states:

$$\Pr(\text{FC}) = \Pr(\text{FC}/\text{C}) \times \Pr(\text{C}) + \Pr(\text{FC}/\bar{\text{C}}) \times \Pr(\bar{\text{C}})$$

$$\text{and } \Pr(\text{C}) = \Pr(\text{C}/\text{A}) \times \Pr(\text{A}) + \Pr(\text{C}/\bar{\text{A}}) \times \Pr(\bar{\text{A}}), \text{ where}$$

$\Pr(\text{FC})$  = the probability that an HIV-infected person will have cytomegalovirus retinopathy as the first manifestation of AIDS,

$\Pr(\text{FC}/\text{C})$  = the probability that an AIDS patient with cytomegalovirus retinopathy will have had cytomegalovirus retinopathy as the first manifestation of AIDS,

$\Pr(\text{C})$  = the probability that an HIV-infected person will have cytomegalovirus retinopathy,

$\Pr(\text{FC}/\bar{\text{C}})$  = the probability that an AIDS patient without cytomegalovirus retinopathy will have had cytomegalovirus retinopathy as the first manifestation of AIDS,

$\Pr(\bar{\text{C}})$  = the probability that an HIV-infected person does not have cytomegalovirus retinopathy,

$\Pr(\text{C}/\text{A})$  = the probability that an AIDS patient will have cytomegalovirus retinopathy (prevalence of cytomegalovirus retinopathy),

$\Pr(\text{A})$  = the probability that an HIV-infected patient will develop AIDS in a seven-year period,

$\Pr(\text{C}/\bar{\text{A}})$  = the probability that an HIV-infected patient without AIDS will have cytomegalovirus retinopathy, and  
 $\Pr(\bar{\text{A}})$  = the probability that an HIV-infected person will not develop AIDS in a seven-year period.

Because  $\Pr(\text{FC}/\bar{\text{C}})$  and  $\Pr(\text{C}/\bar{\text{A}})$  are necessarily equal to zero, the calculations can be reduced to the following formula:  $\Pr(\text{FC}) = \Pr(\text{FC}/\text{C}) \times \Pr(\text{C}/\text{A}) \times \Pr(\text{A})$ . Using these figures [ $\Pr(\text{FC}/\text{C}) = 0.09$ ;  $\Pr(\text{C}/\text{A}) = 0.20$ ;  $\Pr(\text{A}) = 0.25$ ], the probability that an HIV-infected person will have cytomegalovirus retinopathy as the first manifestation of AIDS [ $\Pr(\text{FC})$ ] within seven years is calculated to be 45%. The true risk may actually be even lower; zidovudine, a drug that has been used extensively only since mid 1987, delays the onset of AIDS.<sup>14</sup> Only two of the 15 patients in this study had used zidovudine.

It is currently estimated that 50% of HIV-infected patients will develop AIDS within 11 years.<sup>15</sup> It would probably be unwise to extrapolate the figures discussed above to this longer time period, however. There may be other factors related to the delayed onset of AIDS that could possibly influence the development of early cytomegalovirus retinopathy as well.

This patient group was selected for study because it was drawn from a well-characterized total population of patients, allowing estimates of frequency. Although the patients were examined several years ago, there is no reason to suspect that the characteristics of this subset of patients have changed recently. Although our previous study<sup>10</sup> documented evidence of increasing survival, there was no evidence that the frequency with which cytomegalovirus retinopathy was the index diagnosis had changed since the first case was seen at UCLA in 1983. Since 1987 when the last patient was entered into this study, we still have not examined a patient with HIV-related cytomegalovirus retinopathy who was otherwise completely asymptomatic (unpublished data). Although this observation may reflect a heightened awareness of the subtle manifestations of HIV infection, we believe it adds support to the conclusions previously discussed.

The calculated rates are obviously gross estimates and may actually be higher or lower than stated. The many potential sources of error in the study include the following: it was performed in a retrospective manner; it studied a nonrandom sample; and estimated probabilities were derived from multiple studies. A larger study would be needed to determine the true incidence of cytomegalovirus retinopathy as



the initial manifestation of AIDS. It should be clear from the data presented, however, that HIV-infected patients without AIDS have a low risk of developing cytomegalovirus retinopathy before other indicator diseases. This finding supports previous statements that cytomegalovirus retinopathy is usually a late manifestation of the syndrome.

Because cytomegalovirus retinopathy is usually a late manifestation of AIDS, it is possible that patients who develop the infection before other indicator diseases will be less likely to have appropriate evaluation of visual symptoms. Conversely, it is impractical for all HIV-infected patients to have frequent routine ophthalmic examinations to screen for cytomegalovirus retinopathy. Nevertheless, early recognition of cytomegalovirus retinopathy is important if antiviral treatment is to be effective for preservation of sight. A better understanding of which patients will develop cytomegalovirus retinopathy as their index diagnosis would therefore be desirable. Such information would also be important because they appear to have a worse prognosis for survival.<sup>10</sup> Unfortunately, this study was unable to identify any unique patient characteristics among the group of nine for whom cytomegalovirus retinopathy was the initial manifestation of AIDS.

Although six of the 15 patients in this study had indicator diseases other than cytomegalovirus retinopathy, their eye infection was the first identifiable disease diagnostic of AIDS. Presumably, some patients postpone seeking medical attention for other AIDS-related illnesses because the associated symptoms are more tolerable than loss of vision. It is therefore important for ophthalmologists to be aware of the spectrum of diseases associated with AIDS and their manifestations. One should suspect other serious, but as yet unidentified, illnesses in HIV-infected patients with cytomegalovirus retinopathy who do not yet have a diagnosis of AIDS. Recognition of such problems, with prompt referral to other specialists, may result in earlier and more successful management of those problems than might otherwise occur.

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#### OPHTHALMIC MINIATURE

Well, consider the skeleton; slender, svelte, economical of line and contour. Exquisitely carved oriental ivory! Perfect, thin as a white praying mantis!

His eyes: weren't they protuberant, ordinary, numb-looking?

Be so kind as to note the eye-sockets of the skull; so deep and rounded, somber, quiet pools, all-knowing, eternal. Gaze deep and you never touch the bottom of their dark understanding. All irony, all life, all everything is there in the cupped darkness.

Ray Bradbury, "Skeleton," *The October Country*  
New York, Ballantine Books, 1967, p. 71



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## Decrease in the Risk of Bilateral Acute Retinal Necrosis by Acyclovir Therapy

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Hilel Lewis, M.D., Gary N. Holland, M.D., William F. Mieler, M.D.,  
Douglas A. Jabs, M.D., and Carolyn Drews, Ph.D.

We reviewed the course of 54 patients who had unilateral acute retinal necrosis at initial examination. Thirty-one patients were treated with acyclovir, whereas 23 were not. Of the 31 patients treated with acyclovir, 27 (87.1%) had fellow eyes that remained disease-free throughout a median follow-up of 12 months. Of the 23 patients not treated with acyclovir, seven (30.4%) had fellow eyes that remained disease-free throughout a median follow-up of 11 months. Survival analysis indicated that the fellow eyes of the group of patients treated with acyclovir were more likely to remain disease-free than the fellow eyes of the group not treated with acyclovir ( $P = .0013$ ). Two years after initial onset, the proportion of fellow eyes that remained disease-free was 75.3% for the group treated with acyclovir and 35.1% for the group not treated with acyclovir. These results suggest that acyclovir treatment reduces the risk of involvement of the fellow eye in patients with acute retinal necrosis.

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**A**CUTE RETINAL NECROSIS is a syndrome characterized by iritis, vitreitis, and vaso-occlusive necrotizing retinitis developing in otherwise healthy patients of all ages. The syndrome was first described in Japanese patients by Urayama and associates<sup>1</sup> in 1971 and subsequently in patients of the United States by Willerson, Aaberg, and Reeser.<sup>2</sup>

Willerson, Aaberg, and Reeser<sup>2</sup> suggested that the herpes simplex virus or the varicella-zoster virus may be the etiologic agent responsible for the retinitis seen in their two patients. More recent reports have confirmed this hypothesis.<sup>3-11</sup> Treatment with the antiviral agent, acyclovir, hastens the resolution of retinal lesions but does not appear to prevent the development of retinal detachment and subsequent ocular complications.<sup>12</sup>

At least one third of patients with acute retinal necrosis develop bilateral disease. In most instances, the fellow eye becomes involved within six weeks of the onset of symptoms in the first eye.<sup>13</sup> The fellow eye, however, may become involved years after the initial inflammation.<sup>4,12,14</sup> The purpose of this study was to examine the potential protective effect of acyclovir treatment on the fellow eye in patients with the acute retinal necrosis syndrome. We studied long-term follow-up of 54 patients who had unilateral acute retinal necrosis at initial examination. Thirty-one of these patients were treated with acyclovir, whereas 23 were not.

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### Patients and Methods

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A review was conducted at the Bascom Palmer Eye Institute, the Emory Eye Center, the Jules Stein Eye Institute, the Medical College of Wisconsin, and the Wilmer Eye Institute to identify

patients with acute retinal necrosis. A total of 73 patients with acute retinal necrosis were seen between January 1976 and August 1989. In all cases, the diagnosis of acute retinal necrosis was established on the basis of the characteristic confluent peripheral vaso-occlusive necrotizing retinitis accompanied by varying degrees of anterior segment and vitreous inflammation. None of these patients had the acquired immunodeficiency syndrome or were considered to be immunocompromised in any other way.

Of the 73 patients with acute retinal necrosis, 16 had bilateral disease when first seen and were excluded from the study. Three patients with previous retinal detachment in the fellow eye were excluded (one with toxoplasmosis, one with cysticercosis, and one who was blind from retinal detachment).

The gender, age, date of onset of acute retinal necrosis, history of systemic corticosteroid treatment, history of acyclovir treatment, date of onset of acute retinal necrosis in the fellow eye, and date of last follow-up of all patients were collected. Systemic corticosteroid use is defined as the use of orally administered prednisone, intravenously administered methylprednisolone, or both. Patients who received periocular corticosteroid injections or corticosteroid eyedrops were not included in the systemic corticosteroid-treated group. In most patients, acyclovir was initially administered intravenously (1,500 mg/m<sup>2</sup>/day) for seven to ten days and then orally for two to four weeks.

The relative risk of developing acute retinal necrosis in the fellow eye was initially estimated, using Fisher's exact chi square. Generalized Wilcoxon-test statistics and Kaplan-Meier curves were used to evaluate the effect of treatment on the development of acute retinal necrosis in the fellow eye. Cox proportional hazards models assessed the effect of acyclovir on the incidence rate of acute retinal necrosis in the fellow eye, and simultaneously controlled for age, gender, calendar year, and systemic corticosteroid use.

## Results

Fifty-four patients with unilateral acute retinal necrosis were included in this study. Thirty-one patients were treated with acyclovir, whereas 23 patients were not. The average age for the group treated with acyclovir was 43 years and was 41 years for the group not treated

**TABLE 1**  
BASELINE CHARACTERISTICS OF PATIENTS WITH  
UNILATERAL ACUTE RETINAL NECROSIS

CHARACTERISTIC	ACYCLOVIR-TREATED GROUP (N = 31)	GROUP NOT TREATED WITH ACYCLOVIR (N = 23)
	NO. (%)	NO. (%)
Age (yrs)		
< 20	5 (16.7)	4 (17.4)
20 to 39	9 (30.0)	7 (30.4)
40 to 59	7 (23.4)	9 (39.1)
≥ 60	9 (30.0)	3 (13.0)
Average age	43	41
Sex		
Male	21 (67.7)	11 (47.8)
Female	10 (32.3)	12 (52.2)
Patients treated with systemic corticosteroids	23 (74.2)	14 (60.8)
Patients seen after 1981	31 (100)	6 (26.0)

with acyclovir (Table 1). Twenty-one of the 31 patients (67.7%) in the group treated with acyclovir were male and 11 of the 23 patients (47.8%) in the group not treated with acyclovir were male. Twenty-three of the 31 patients (74.2%) treated with acyclovir were treated with systemic corticosteroids, whereas 14 (60.8%) of the 23 patients not treated with acyclovir were treated with systemic corticosteroids. All of the patients treated with acyclovir were seen after 1981, whereas only six of the 23 patients (26.0%) not treated with acyclovir were seen after 1981. As evidence implicating a virus of the herpes group as the etiologic agent became available, acyclovir treatment was more likely to be given to patients who developed acute retinal necrosis after 1981.

Of the 31 patients treated with acyclovir, 27 (87.1%) were disease-free in the fellow eye at the last visit (Table 2). Fifteen of these 27 patients (55.6%) were seen at least one year after the onset, and six of these 27 patients (22.2%) were seen at least two years after the onset. Of the 23 patients not treated with acyclovir, only seven (30.4%) were disease-free in the fellow eye at the last visit. Three of these seven patients (42.8%) were seen at least one year after the onset, and three of these seven patients (42.8%) were seen at least two years after the onset. For patients whose disease

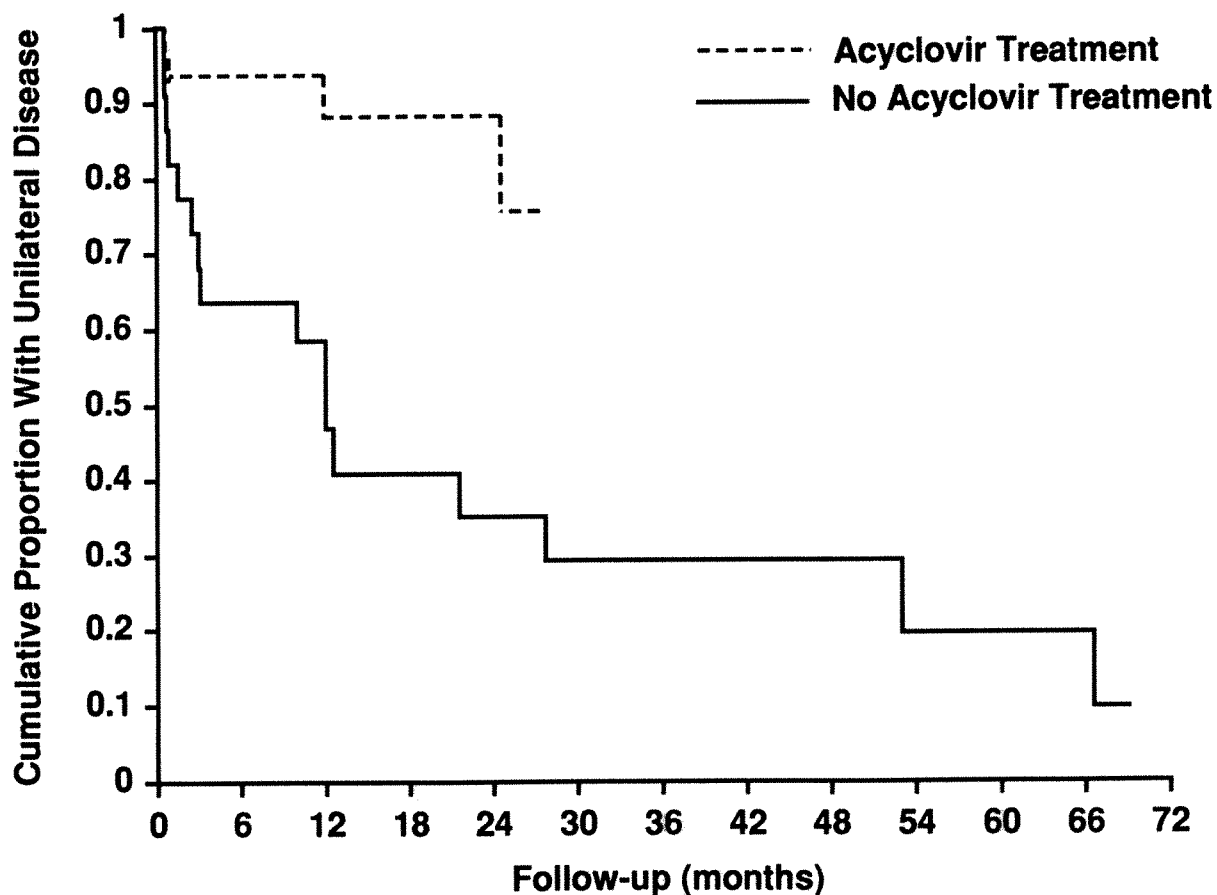


**TABLE 2**  
NUMBER OF PATIENTS WITH UNILATERAL DISEASE  
WHEN LAST EXAMINED

	ACYCLOVIR-TREATED GROUP (N = 31)	GROUP NOT TREATED WITH ACYCLOVIR (N = 23)
	NO. (%)	NO. (%)
Patients with unilateral disease at last follow-up visit	27 (87.1)	7 (30.4)
Patients with unilateral disease monitored for at least 1 yr	15 (55.6)	3 (42.8)
Patients with unilateral disease monitored for at least 2 yrs	6 (22.2)	3 (42.8)
Median follow-up (mos) of unilateral cases	12.0	11.0

remained unilateral at the last known visit, the median follow-up for the group treated with acyclovir was 12 months and 11 months for the group not treated with acyclovir. The range of follow-up for the group treated with acyclovir was 0.5 to 89.3 months and 0.5 to 137.0 months for the group not treated with acyclovir.

A survival analysis (Figure) displays the survival curve estimate of the cumulative proportion of patients who remained disease-free in the fellow eye. The group of patients treated with acyclovir was less likely than the group not treated with acyclovir to develop acute retinal necrosis in the fellow eye ( $P = .0013$ ). At one year, the cumulative proportion of patients who remained disease-free in the fellow eye was 87.8% for the group treated with acyclovir and 46.8% for the group not treated with acyclovir. The terminal point in each survival curve occurred when the last patient in each group developed bilateral disease. For the



**Figure** (Palay and associates). Estimate of the cumulative proportion of patients with unilateral disease at a given point in time for the group of patients treated with acyclovir and for the group of patients not treated with acyclovir.

group treated with acyclovir, this was approximately two years, and for the group not treated with acyclovir this was approximately 5½ years. Therefore, the last follow-up time by which the two groups can be compared directly is two years. At two years, the cumulative proportion of patients who remained disease-free in the fellow eye is 75.3% for the group treated with acyclovir and 35.1% for the group not treated with acyclovir.

The protective effect of acyclovir treatment appears to be most pronounced during the first 14 weeks of treatment, as this is the time during which the greatest divergence between the two survival curves occurs. In the group of patients treated with acyclovir, there were two cases of bilateral involvement within the first 14 weeks of treatment, whereas in the group of patients not treated with acyclovir, there were eight cases of bilateral involvement within the first 14 weeks of treatment.

The rate at which the fellow eye became involved in patients treated with acyclovir was 17% (95% confidence interval = 4% to 79%) of the rate at which the fellow eye became involved in patients not treated with acyclovir, even when controlling for corticosteroid use (Table 3). The rate at which the fellow eye became involved in patients treated with systemic corticosteroids was 70% (95% confidence interval = 28% to 176%) of the rate at which the fellow eye became involved in patients not treated with systemic corticosteroids, even when controlling for acyclovir use. Thus, acyclovir treatment, independent of systemic corticosteroid use, appeared to prevent the develop-

ment of acute retinal necrosis in the fellow eye. However, the possibility that systemic corticosteroid treatment had a beneficial or detrimental effect on the development of bilateral disease could not be completely excluded.

## Discussion

Our study demonstrates that acyclovir treatment decreases the rate of bilateral involvement in patients who have unilateral acute retinal necrosis at initial examination ( $P = .0013$ ). The rate at which the fellow eye became involved in patients treated with acyclovir was 17% of the rate at which the fellow eye became involved in patients not treated with acyclovir, even when controlling for systemic corticosteroid use. The effect of acyclovir was most pronounced during the first 14 weeks after initial examination, as this was the time period during which the greatest divergence between the two survival curves occurred.

The risk of infection of the fellow eye may be greatest in the first few weeks after involvement of the first eye because the replicating virus may spread from one eye to the other during this time. Experimental and clinical evidence to support this hypothesis is available. In mice, intraocular injection of herpes simplex virus type 1 results in a necrotizing retinitis in the contralateral eye within seven to ten days, whereas the injected eye remains disease-free.<sup>15</sup> Histologic staining for an indicator enzyme shows viral progression from the iris and ciliary body of the injected eye down the parasympathetic neurons and into the nuclei of the visual system in the brain. Ultimately, there is infection of the contralateral retina via the optic nerve over a nine- to ten-day course.<sup>16</sup> One case, included in this study as a recurrence in the fellow eye after two years, was initially reported by Lewis and associates<sup>10</sup> to have magnetic resonance imaging findings suggestive of a retrograde spread of virus to both optic tracts and the lateral geniculate ganglia. The fellow eye developed retinitis despite long-term prophylactic treatment with acyclovir. Such late involvement of the fellow eye may represent reactivation of latent virus that had already reached the visual pathways of the fellow eye during the initial infection. In this case, herpes simplex type 1 was cultured from the intraocular fluids of the first eye.

The exact mechanism of the protective effect

**TABLE 3**  
RELATIVE RATE OF BILATERAL ACUTE RETINAL  
NECROSIS IN PATIENTS TREATED WITH ACYCLOVIR  
OR SYSTEMIC CORTICOSTEROIDS

	RATE	95% CONFIDENCE INTERVAL
Relative rate of bilateral involvement in patients treated with acyclovir vs patients not treated with acyclovir (controlling for systemic corticosteroid use)	17%	4% to 79%
Relative rate of bilateral involvement in patients treated with systemic corticosteroids vs patients not treated with systemic corticosteroids (controlling for acyclovir use)	70%	28% to 176%



of acyclovir on the fellow eye seen in this study is unknown. Intravenously administered acyclovir has been shown to decrease viral shedding in the tears of herpes simplex-infected rabbits, but it does not eradicate established latent herpes infection.<sup>17</sup> After the cessation of systemic acyclovir treatment, viral shedding recurs, presumably because of reactivation of the latent virus.<sup>18</sup> Acyclovir is only effective against the actively replicating virus and has no proven effect on the latent form of the virus.<sup>19</sup> The reactivation of herpes infection after the discontinuance of acyclovir treatment has been observed in humans as well. Long-term suppression therapy with acyclovir in immunocompetent adults suffering from genital herpes<sup>20,21</sup> and in patients with recalcitrant herpes simplex keratitis,<sup>22</sup> reduces the frequency of reactivation of herpetic disease, but once acyclovir treatment is discontinued, reactivation of disease occurs. It is probable that the protective effect of acyclovir demonstrated in this study is related to suppression of viral infection in the first few weeks of treatment, the time in which the risk of developing bilateral disease is greatest. Once acyclovir treatment is discontinued, a latent viral state probably exists and the continued protective effect on the fellow eye is less certain.

Because of the strong protective effect of acyclovir on the fellow eye shown in this study, we recommend that as soon as the condition is suspected, patients with acute retinal necrosis should be treated with intravenously administered acyclovir 1,500 mg/m<sup>2</sup>/day for seven to ten days. Because the risk of bilateral involvement is greatest in the first 14 weeks, we recommend treatment with orally administered acyclovir (800 mg five times daily) for up to 14 weeks after intravenous treatment. We do not currently recommend routine long-term prophylaxis. Late occurrences of bilateral disease in the fellow eyes of patients with acute retinal necrosis who receive initial acyclovir treatment appear to be uncommon and the effectiveness of long-term prophylaxis is uncertain.

A beneficial effect of corticosteroid treatment on the incidence of bilateral disease could not be demonstrated in this study. Because treatment of the intense inflammatory reaction of the infected eye may be beneficial, we now routinely treat all patients with periocular or systemic corticosteroids, or both, within the first 24 hours of beginning acyclovir treatment. Systemic corticosteroid treatment is tapered during the time that the orally administered

acyclovir is being reduced. Additional study will be necessary to determine the optimal duration of acyclovir treatment and to conclude whether corticosteroid treatment reduces the ocular morbidity of this devastating ocular infection.

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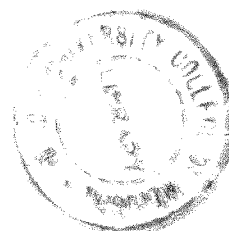
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#### OPHTHALMIC MINIATURE

But it was the cold aquamarine glitter of her eyes enclosed in a harsh fretwork of lines that arrowed out toward her temples which drew my most breathless attention; they were like the rays of the sun in a child's drawing.

Pat Conroy, *The Prince of Tides*  
New York, Bantam Books, 1986, p. 229





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# Retinal Function and Rhodopsin Levels in Autosomal Dominant Retinitis Pigmentosa With Rhodopsin Mutations

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and Jeremy Nathans, M.D.

We studied rod and cone function in 20 patients from six families with autosomal dominant retinitis pigmentosa, who represented five different point mutations in the gene encoding rhodopsin. In a family with a stop codon mutation at the carboxyl end of the molecule (glutamine-344), young members with the mutation were asymptomatic and clinically unaffected but showed about 1 log unit of rod sensitivity loss across the visual field and decreased rhodopsin levels; at this stage, cone function was essentially normal. In three families with mutations at the border of a transmembrane segment (arginine-135-leucine and arginine-135-tryptophan), there was neither detectable rod function nor measurable rhodopsin; cone function was variably impaired. Two families carrying different mutations (threonine-17-methionine and threonine-58-arginine) had altitudinal visual field defects with less impaired rod and cone function in the inferior than in the superior field. Rod adaptation was abnormal in both families, but the time course of adaptation differed between patients with the two mutations. Differences in the pattern of retinal dysfunction were therefore discernible in patients with different rhodopsin mutations.

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**M**OLECULAR GENETIC STUDIES of families with autosomal dominant retinitis pigmentosa have led to the discovery of mutations in the gene encoding rhodopsin, the visual pigment of the rod photoreceptor, and these rhodopsin mutations correlate with the presence of retinal degeneration.<sup>1-8</sup> The number of point mutations of the rhodopsin gene identified by molecular geneticists has increased, but our understanding of the expression of the retinal disease in patients with the different mutations has not kept pace. Detailed descriptions of the ocular examination of patients have been published for two mutations.<sup>9-11</sup> The findings with traditional clinical techniques of assessment suggested considerable clinical heterogeneity among patients with a given mutation and differences only in severity between patients with different mutations.<sup>10,11</sup>

We studied the phenotypes of 20 affected members of six families with autosomal dominant retinitis pigmentosa, who represented five different point mutations of the rhodopsin gene.<sup>5</sup> In addition to traditional ocular examination methods and electroretinography, we studied the patients with dark- and light-adapted perimetry, dark adaptometry, and imaging fundus reflectometry, techniques used in earlier studies that found different functional subtypes of autosomal dominant retinitis pigmentosa.<sup>12-18</sup> Our results indicated discernible differences in the pattern of retinal dysfunction between families with different mutations, and that three families with mutations at the same amino acid position showed a similar functional phenotype.

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## Patients and Methods

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Twenty patients, representing six families with autosomal dominant retinitis pigmentosa, were included in this study. These patients and

their families had a rhodopsin gene mutation identified in an earlier molecular genetic investigation that found 13 different point mutations at 12 amino acid positions.<sup>5</sup>

The six families represented five different rhodopsin gene mutations; there are four amino acid substitutions and a stop codon mutation that produced a truncated protein. Amino acid substitutions are designated by a letter representing the amino acid usually present at that position, followed by the number of the position, followed by the amino acid present in the mutant rhodopsin. The amino acid substitutions are as follows: threonine-17-methionine (T17M); threonine-58-arginine (T58R); arginine-135-leucine (R135L); and arginine-135-tryptophan (R135W). The stop codon mutation is at glutamine-344 (Q344\*).

All patients were examined clinically, with traditional clinical measures of visual function (Goldmann kinetic perimetry and full-field rod and cone electroretinography), and with dark- and light-adapted static threshold perimetry. A subset of patients was also studied with dark adaptometry and imaging fundus reflectometry. Informed consent was given by all subjects after a full explanation of the procedures was provided.

Goldmann kinetic visual fields were performed in both eyes of all patients using targets V (64 mm<sup>2</sup> area) and I (0.25 mm<sup>2</sup> area) at intensity 4e (318 candelas per square meter) on the 10-cd/m<sup>2</sup> white background. Test targets were moved from nonseeing to seeing areas. The visual fields were quantified by computer and results are expressed as a percent of the normal mean value.<sup>19,20</sup> Full-field rod and cone electroretinography was performed in one eye of all patients according to previously described methods.<sup>19,21</sup>

Static threshold perimetry was performed in one eye of all patients in the dark- and light-adapted states using monochromatic stimuli (target area, 64 mm<sup>2</sup>) to measure rod- and cone-mediated function across the visual field. Dark-adapted perimetry was performed with 650- and 500-nm targets and light-adapted (10 cd/m<sup>2</sup>) perimetry with a 600-nm target. Instrumentation, technique, analysis methods, and normal results have been described.<sup>20-23</sup> The two test strategies used were a full-field test of 75 loci (12-degree grid) and a horizontal-profile test (at 2-degree spacing) in the central 60 degrees. For the dark-adapted testing, the sensitivity difference between the 500- and 650-nm stimuli at each test locus

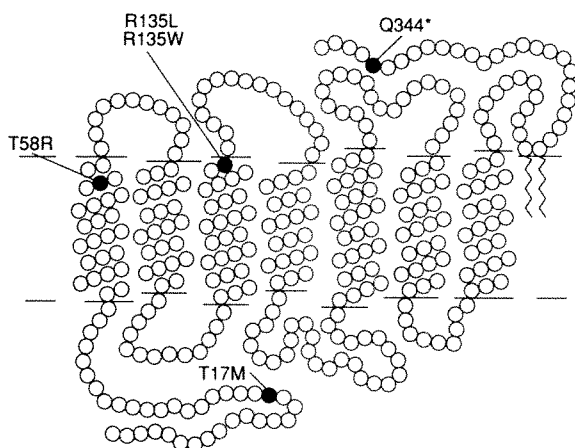
determined if rods, cones, or both were mediating detection of the stimulus.<sup>12,22,23</sup> Sensitivity losses were calculated for rods (on the basis of 500-nm test results, dark adapted) and for cones (on the basis of 600-nm test results, light adapted) by comparison to mean values of normal subjects.<sup>20</sup>

Dark adaptometry was performed at 36 degrees in the inferior visual field with 500- and 650-nm stimuli (target area, 64 mm<sup>2</sup>), using methods like those previously reported.<sup>21,24</sup> The yellow bleaching light, which was of intensity 5.6 log scotopic trolands and a duration of one minute (expected to bleach about 90% of the rhodopsin in the region of the retina exposed to the light in the normal eye<sup>25</sup>), was delivered with a Zeiss fundus camera to a 30-degree-diameter region centered 36 degrees superior in the retina to fixation. Prebleach baseline dark-adapted (more than three hours) thresholds were established at two sessions, preceding the adaptometry sessions on days when there was no exposure to bright light.<sup>26</sup>

Imaging fundus reflectometry was performed with instrumentation and procedures already described.<sup>14,16,27</sup> Images of the retina were obtained (on a high-sensitivity television system attached to a Zeiss fundus camera) when it was illuminated with dim monochromatic measuring lights at a sequence of several different wavelengths. The luminance levels of the retinal images of the fully light-adapted eye were compared to those obtained when the eye was allowed to adapt to the dark. The density change (the differences of the logarithms of the reflectance values obtained for the two conditions) gives a measure of the level of visual pigment regeneration that accompanied dark adaptation. In the procedure, the subject (with fully dilated pupil) was aligned with the instrument, with head position stabilized by means of a bite-bar and forehead rests. Fixation was ipsilateral, using a small red fixation target arranged so that the area of retina under test was the midperiphery (usually centered on 30 degrees temporal to the fovea). The subject was then light adapted with a yellow light of intensity 6.05 log scotopic trolands delivered for a period of one minute to an area of retina concentric with, but larger than, the test area. Images of the test area of the retina were collected for up to 45 minutes after the bleaching exposure.

Additional two-color dark-adapted static perimetric measurements were made at 25 locations on a rectangular grid covering an area of





**Fig. 1** (Jacobson and associates). Schematic drawing of a rhodopsin molecule in the membrane (broken horizontal lines) of the rod photoreceptor outer segment. Single amino acids are shown as circles. The filled circles with labels are the sites of amino acid changes resulting from point mutations of the rhodopsin gene in the patients in this study. The amino acid substitutions are as follows: T17M, threonine-17-methionine; T58R, threonine-58-arginine; R135L, arginine-135-leucine; and R135W, arginine-135-tryptophan. A stop codon mutation at glutamine-344 is represented as Q344\*.

retina of  $30 \times 30$  degrees. The test region was centered in the midperiphery of the temporal retina to correspond with the area within which rhodopsin measurements were made.

## Results

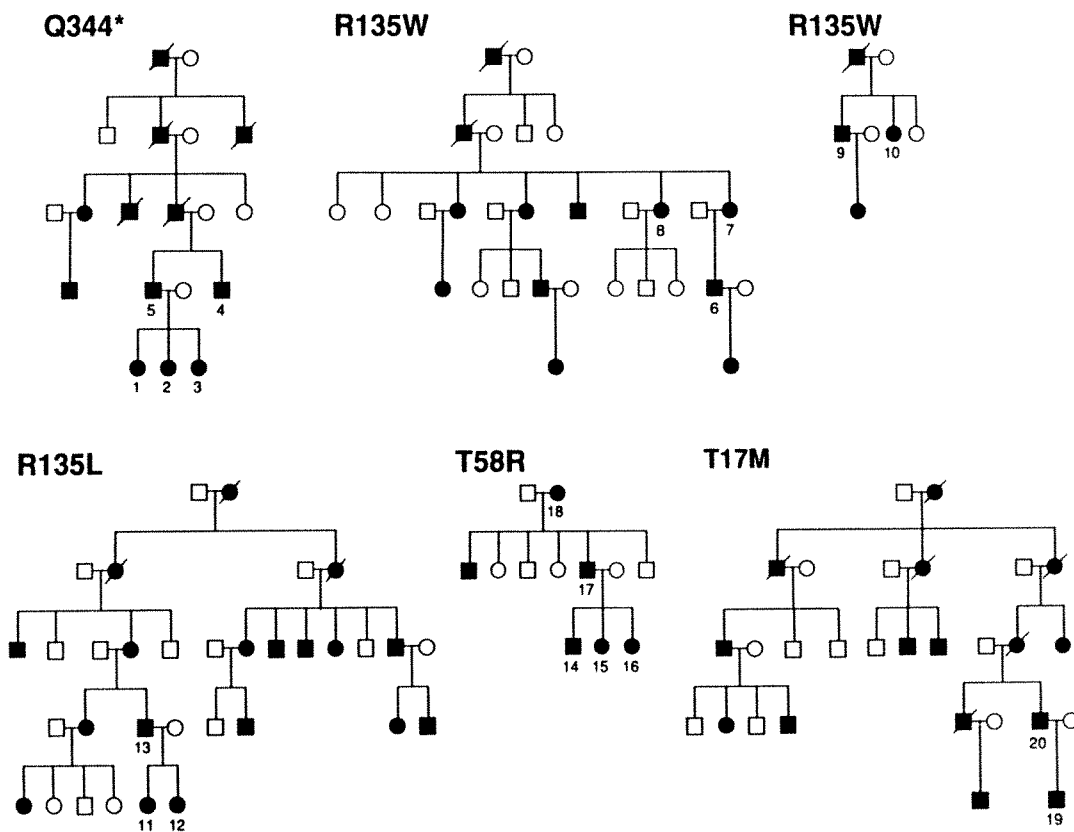
Figure 1 is a schematic drawing of the rhodopsin molecule showing the sites of the amino acid substitutions in the families with autosomal dominant retinitis pigmentosa in this study. Each family has at least three generations affected with retinitis pigmentosa and male-to-male transmission, confirming the autosomal dominant inheritance of the disease (Fig. 2). The 20 patients we studied with retinal function tests are numbered on the pedigrees and these numbers correspond to the case numbers in Tables 1 and 2.

Patients 1 through 3, the three young women with the Q344\* mutation, had normal visual acuity and a full extent of their kinetic visual fields to the  $V_{4e}$  and  $I_{4e}$  targets (Table 1). These three patients also had normal-appearing fundi on ophthalmoscopy. The other 17 patients varied in the degree of visual acuity impairment

but all showed reduced extent of their visual fields to the  $I_{4e}$  target only or to both targets. On ophthalmoscopic examination, the two older members of the family with the Q344\* mutation (Patients 4 and 5), and all eight members of the families with Arg-135 (R135L and R135W) mutations showed retinal vessel attenuation and pigmentary abnormalities in the superior and inferior retina. In the seven patients with T58R and T17M mutations, the pigmentary retinopathy appeared limited to the inferior retina or there were greater abnormalities inferiorly than superiorly. Among the younger patients, cystoid macular changes were evident in Patients 11, 14, 15, and 16.

Electroretinography was performed in the 20 patients (Table 2). The young women with the Q344\* mutation showed reductions in the amplitude of the rod and mixed cone-rod electroretinograms. Cone flicker amplitude in all three sisters was within normal limits, but timing was delayed in two of them. Electroretinograms were not detectable in the more severely affected members with this mutation. All eight patients with Arg-135 mutations had no detectable rod or cone signals, despite computer averaging. Patients from the family with the T58R mutation, except for severely affected Patient 18, had sizable rod and cone signals that were reduced in amplitude and delayed in timing. Similarly, the electroretinograms in the two patients with the T17M mutation were reduced in amplitude and delayed in timing.

To demonstrate different patterns and degrees of severity of visual field loss, kinetic perimetry results from nine patients representing five of the six families are shown in Figures 3 and 4. Patient 2, from the family with the Q344\* mutation, and her sisters (Patients 1 and 3) had normal kinetic fields to both target sizes, but Patients 4 and 5, the uncle and father, were limited to a central island only. Patient 9, a 40-year-old man from one of the families with an R135W mutation, had a normal extent of visual field with the large target but a reduced field with the small target; his sister (Patient 10) had only a central island. Patients 11 and 12 (two young women, aged 16 and 19 years, respectively) from the family with the R135L mutation already showed considerable visual field loss with the large target and only a central island with the smaller target; their father (Patient 13) had only a central island. In the other family with an R135W mutation, a 45-year-old man (Patient 6) had visual fields similar to that of Patient 11, whereas his mother



**Fig. 2** (Jacobson and associates). Pedigrees of the six families with autosomal dominant retinitis pigmentosa in this study. The label above each pedigree designates the amino acid change resulting from the point mutation in the rhodopsin gene of that family (see Figure 1). Filled symbols are family members affected with retinitis pigmentosa and unfilled symbols are unaffected members; slashed symbols are deceased members. The patients examined with retinal function tests in this study are numbered to correspond with case numbers in Tables 1 and 2. These families are designated L (Q344\*), I2 and I1 (R135W), H2 (R135L), D (T58R), and A (T17M) in reference 5.

(Patient 7) and aunt (Patient 8) had only central islands. All patients from the families with the T58R and T17M mutations showed an altitudinal pattern to their visual field loss with greater loss in superior than in inferior fields. The two most severely affected members of these families (Patients 18 and 20) retained mainly an island of function in the inferior field with (Patient 20) or without (Patient 18) a measurable small central island.

Dark- and light-adapted static threshold perimetry in four mildly affected patients with different rhodopsin mutations disclosed different patterns of rod and cone dysfunction (Fig. 5). Patient 2, who carried the Q344\* mutation and had a normal kinetic field (Fig. 3), had between 1.0 and 2.0 log units of rod sensitivity loss (mean, 15.3 dB; standard deviation, 4.7 dB) throughout the visual field but cone sensitivity

that was within 2 standard deviations of the normal mean at all loci tested. Her two sisters (Patients 1 and 3) showed a similar pattern with mean rod sensitivity losses of 12 dB (standard deviation, 4.9 dB) and 10 dB (standard deviation, 2.7 dB), respectively, and no cone sensitivity losses. Patient 9, who carried the R135W mutation, had no measurable rod sensitivity throughout the visual field and considerable cone sensitivity loss (mean, 14.5 dB; standard deviation, 3.2 dB). Patients 14 and 19, representing the T58R and T17M mutations respectively, both had altitudinal field defects by kinetic perimetry and showed greater rod-sensitivity and cone sensitivity losses in the superior than in the inferior field. At the foveal locus, Patient 19 had normal cone and rod sensitivity, whereas Patient 14 had normal cone sensitivity, but no measurable rod sensi-



TABLE 1  
CLINICAL CHARACTERISTICS OF THE PATIENTS

PATIENT NO.	RHODOPSIN MUTATION	AGE (YRS)	GENDER	VISUAL ACUITY	KINETIC VISUAL FIELD EXTENT (%) <sup>‡</sup>	
					V <sub>4e</sub>	I <sub>4e</sub>
1	Q344*	24	F	R.E.: 20/20	98	96
				L.E.: 20/20	94	92
2	Q344*	26	F	R.E.: 20/20	100	100
				L.E.: 20/20	100	100
3	Q344*	27	F	R.E.: 20/20	100	100
				L.E.: 20/20	100	100
4	Q344*	44	M	R.E.: 20/25*	3	1
				L.E.: 20/30*	3	< 1
5	Q344*	50	M	R.E.: 20/100†	< 1	< 1
				L.E.: 20/200†	< 1	< 1
6	R135W	45	M	R.E.: 20/30†	16	1
				L.E.: 20/25†	14	1
7	R135W	69	F	R.E.: 20/200*	1	< 1
				L.E.: 20/60†	1	< 1
8	R135W	66	F	R.E.: Hand motion†	—	—
				L.E.: Hand motion†	—	—
9	R135W	40	M	R.E.: 20/25*	100	2
				L.E.: 20/30*	94	3
10	R135W	42	F	R.E.: 20/100*	3	2
				L.E.: 20/100*	3	1
11	R135L	16	F	R.E.: 20/30	20	1
				L.E.: 20/40	20	1
12	R135L	19	F	R.E.: 20/30	48	1
				L.E.: 20/30	54	1
13	R135L	48	M	R.E.: 20/30†	1	—
				L.E.: 20/30†	1	< 1
14	T58R	19	M	R.E.: 20/40	100	46
				L.E.: 20/40	100	41
15	T58R	23	F	R.E.: 20/25	68	35
				L.E.: 20/50	61	30
16	T58R	26	F	R.E.: 20/25	100	51
				L.E.: 20/20	94	53
17	T58R	52	M	R.E.: 20/20	65	13
				L.E.: 20/20	60	17
18	T58R	78	F	R.E.: 2/200*	6	—
				L.E.: No light perception†	—	—
19	T17M	35	M	R.E.: 20/20	61	49
				L.E.: 20/20	63	50
20	T17M	67	M	R.E.: 9/200**	37	6
				L.E.: 4/200**	32	6

\*Indicates cataract.

†Indicates aphakia or pseudophakia.

‡Indicates glaucoma.

§Expressed as a percent of normal mean; 2 S.D. below normal = 90% for V<sub>4e</sub> and 88% for I<sub>4e</sub>.

TABLE 2  
ELECTRORETINOGRAPHY RESULTS OF THE PATIENTS

PATIENT NO.	ROD* ELECTRORETINOGRAM		MIXED CONE-ROD† ELECTRORETINOGRAM		CONE-FLICKER‡ ELECTRORETINOGRAM	
	AMPLITUDE (μV)	TIMING (MSEC)	AMPLITUDE (μV)	TIMING (MSEC)	AMPLITUDE (μV)	TIMING (MSEC)
1	130	87	250	54	72	28
2	140	94	Not available		73	30
3	113	86	320	54	66	34
4	Not detectable		Not detectable		Not detectable	
5	Not detectable		Not detectable		Not detectable	
6	Not detectable		Not detectable		Not detectable	
7	Not detectable		Not detectable		Not detectable	
8	Not detectable		Not detectable		Not detectable	
9	Not detectable		Not detectable		Not detectable	
10	Not detectable		Not detectable		Not detectable	
11	Not detectable		Not detectable		Not detectable	
12	Not detectable		Not detectable		Not detectable	
13	Not detectable		Not detectable		Not detectable	
14	120	84	266	56	23	33
15	125	89	180	56	25	33
16	78	92	188	61	43	35
17	86	95	195	56	54	33
18	Not detectable		Not detectable		Not detectable	
19	100	88	258	57	54	33
20	30	102	73	63	17	43

\*Normal amplitude mean equals 299 μV, S.D. equals 52 μV; normal timing mean equals 76 msec, S.D. equals 5 msec.

†Normal amplitude mean equals 497 μV, S.D. equals 111 μV; normal timing mean equals 48 msec, S.D. equals 6.5 msec.

‡Normal amplitude mean equals 98 μV, S.D. equals 24 μV; normal timing mean equals 27 msec, S.D. equals 1.0 msec.

tivity. Rod sensitivity appeared to be severely affected and cone sensitivity appeared to be mildly affected in a wide region of the central field of Patient 14 (analyzed in more detail in Fig. 7), whereas Patient 19 showed only minimal rod sensitivity losses along and below the horizontal meridian.

Two-color dark-adapted perimetry profiles for normal subjects and for patients with the Q344\* and the Arg-135 mutations are shown in Figure 6. Extrafoveal sensitivity levels of normal subjects varied between 60 and 70 dB for the 500-nm target and between 30 and 40 dB for the 650-nm target. Except in the central few degrees, normal subjects had rod photoreceptor mediation of detection (both colors detected by the rod system; sensitivity difference between colors,  $\geq 28$  dB); centrally, mixed rod and cone mediation is possible (500 nm detected by rods and 650 nm by cones; sensitivity difference between 13 and 27 dB<sup>23</sup>). In Patient 3 (Q344\* mutation), rod sensitivity beyond the central few degrees was only slightly reduced

below normal, many loci being mixed rather than rod mediated; central loci showed greater rod sensitivity losses and cone mediation (both colors detected by the cone system; sensitivity difference is  $\leq 12$  dB). A more advanced stage of this disease was exemplified by Patient 4, Patient 3's uncle, who had at least 3 log units of rod sensitivity loss and only cone mediation in his residual central island. At fixation, cone sensitivity to 650 nm was within 2 standard deviations of the mean normal value (determined during the cone plateau of dark adaptation), but at the extrafoveal loci it was abnormally reduced.

All eight patients from the three families with Arg-135 mutations had no measurable rod sensitivity with two-color dark-adapted perimetry. Patient 9, illustrating the mildest degree of expression among the patients examined, had only cone-mediated detection of the two colors and cone sensitivity to 650 nm was normal only in the central few degrees. Patient 6 had only two central loci with normal cone sensitivity,



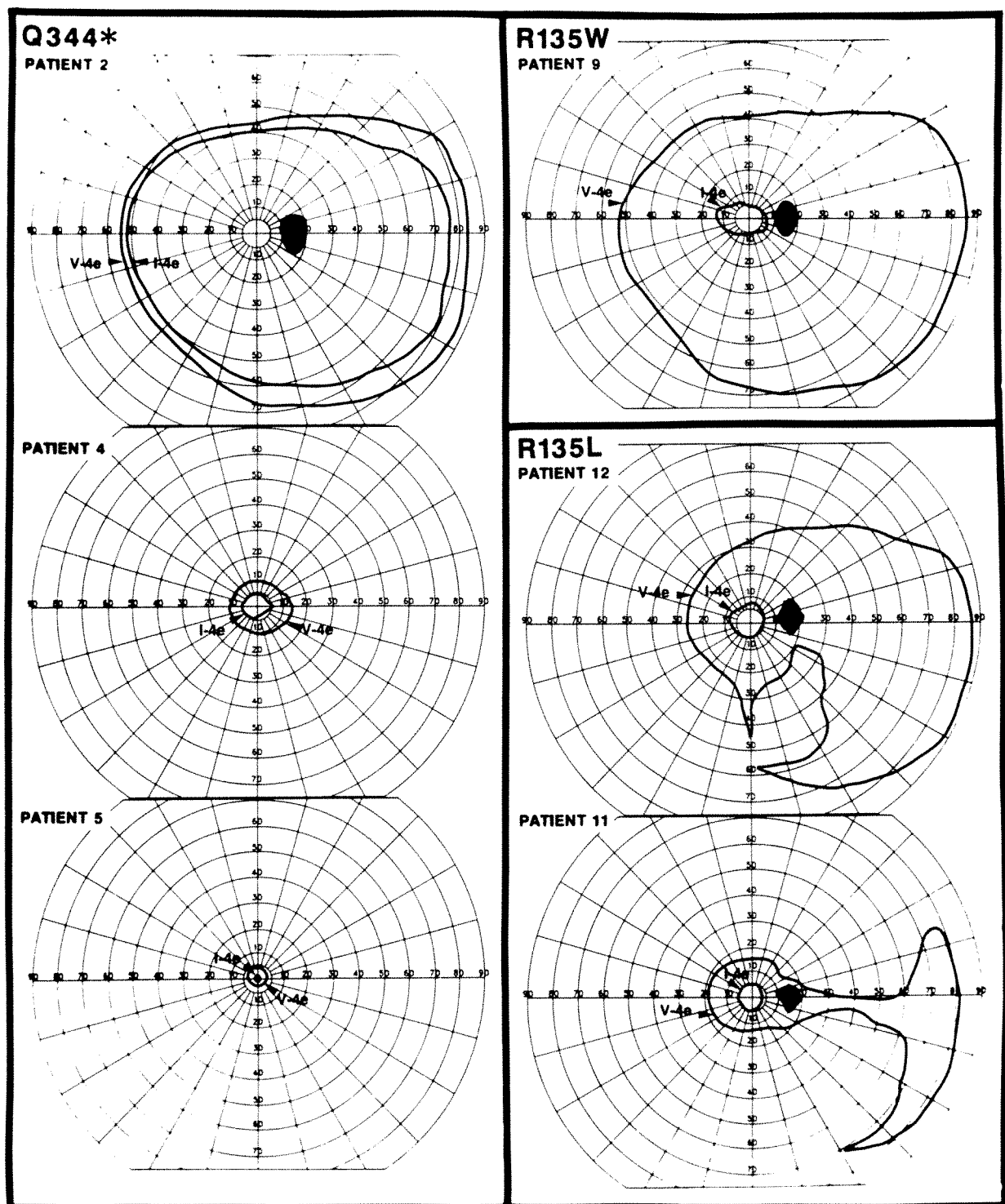


Fig. 3 (Jacobson and associates). Kinetic visual fields to  $V_{4e}$  and  $I_{4e}$  test targets in the right eyes of Patients 2, 4, and 5 with the Q344\* mutation; Patient 9 with the R135W mutation; and Patients 12 and 11 with the R135L mutation.

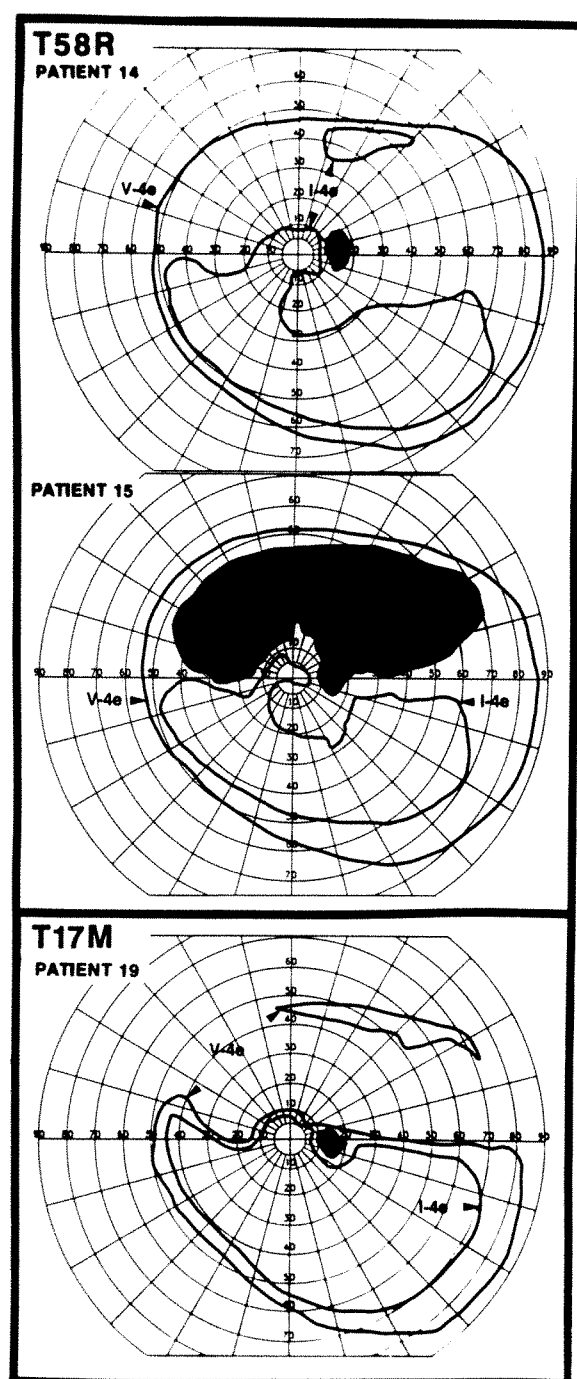


Fig. 4 (Jacobson and associates). Kinetic visual fields to  $V_{4e}$  and  $I_{4e}$  test targets in the right eyes of Patients 14 and 15 with the T58R mutation; and Patient 19 with the T17M mutation.

whereas his mother, Patient 7, had only a small central island of abnormally reduced cone sensitivity. Therefore, at certain stages of disease, the phenotypes of patients with the Q344\*

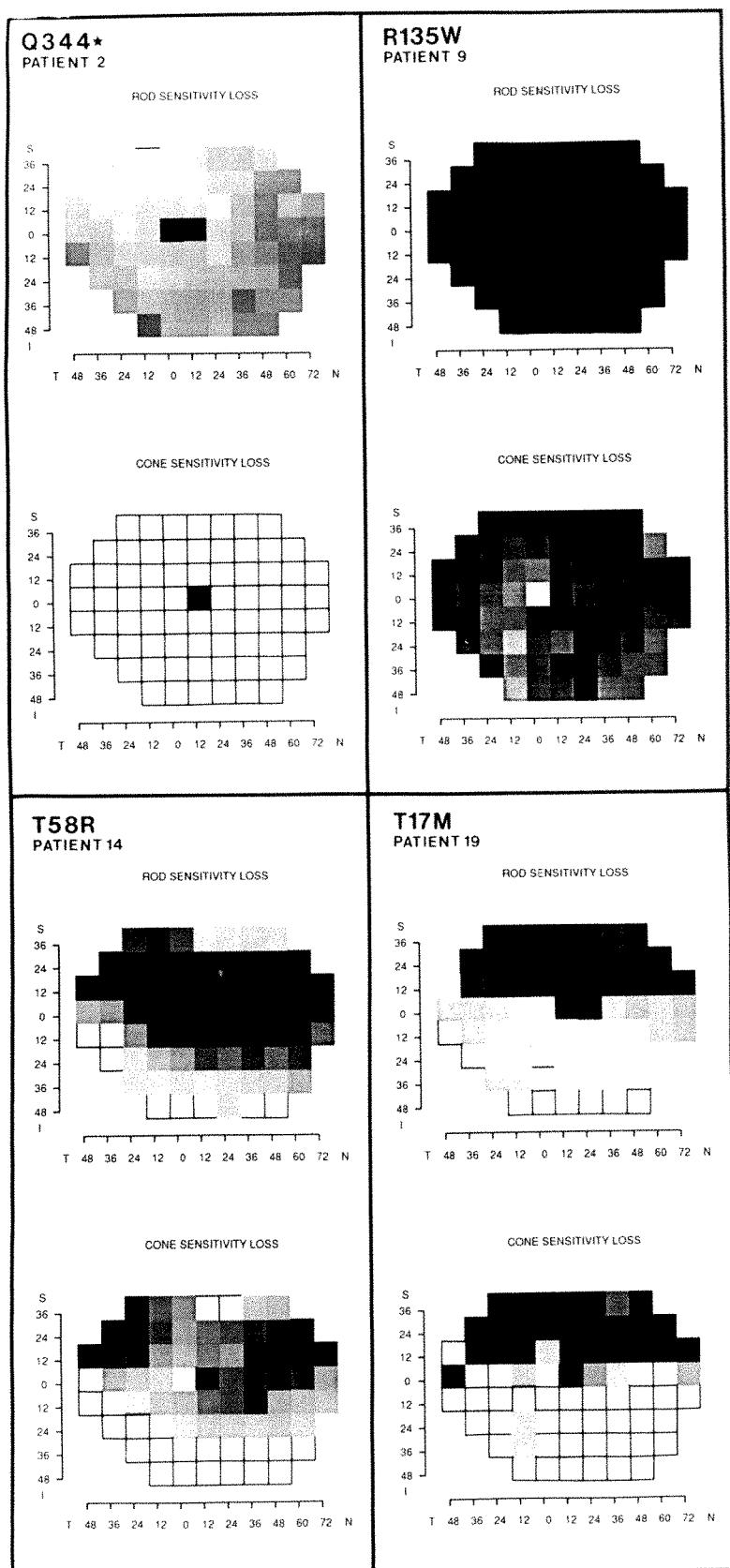
(Patient 4) and Arg-135 (Patient 6) mutations were not distinguishable by dark-adapted perimetry (Fig. 6), electroretinography (Table 2), or clinical features.

In patients from the families with T58R and T17M mutations, visual function appeared similar on the basis of altitudinal visual field defects (Fig. 4) and sizable rod and cone electroretinograms (Table 2). However, testing with two-color dark-adapted perimetry and dark adaptometry yielded distinct differences in central and peripheral retinal function between the two families.

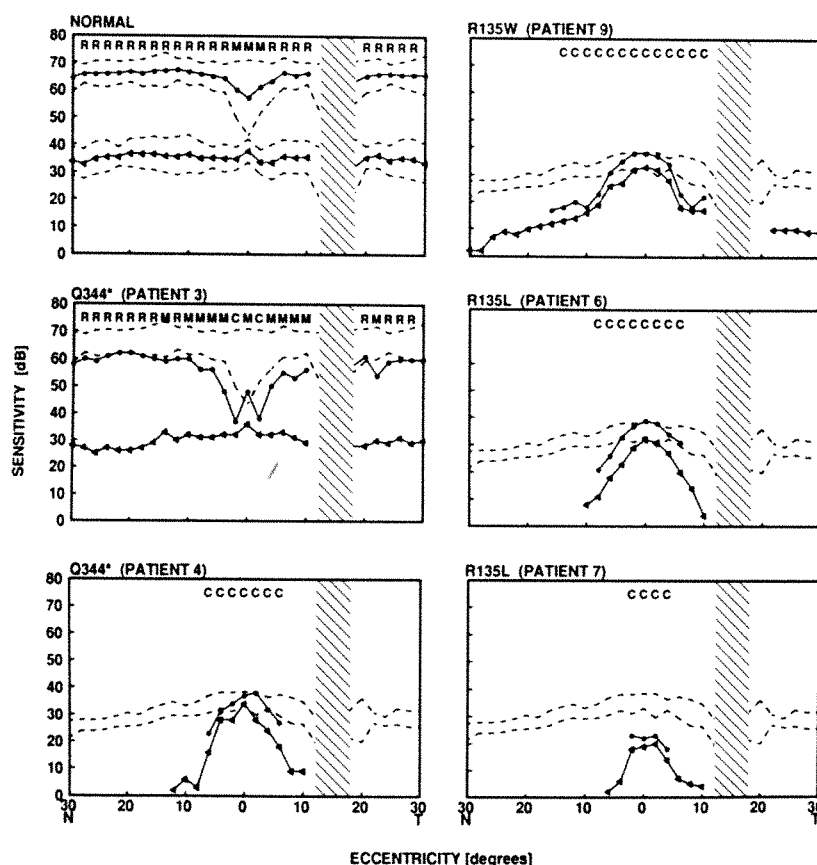
A difference in central function in the two families was detected with two-color dark-adapted perimetric profiles (Fig. 7). In the family with the T58R mutation, Patient 14 (age, 19 years) and his father, Patient 17 (age, 52 years), had no measurable rod sensitivity and abnormally reduced cone sensitivity at almost all loci. This same pattern was observed in Patients 15 and 16 of this family; Patient 18's vision was too poor to test. In contrast, Patient 19 (age, 35 years), from the family with the T17M mutation, had rod- or mixed rod- and cone-mediated sensitivity throughout the central field. Normal or nearly normal rod sensitivity in the central few degrees with increasing rod sensitivity loss at greater eccentricities was observed. This difference in central function between the mutations is further demonstrated in Figure 7 by spectral sensitivity measurements in the dark-adapted state at 12 degrees in the inferior field, a locus within the region traditionally tested for final dark-adapted thresholds.<sup>10,11</sup> The spectral sensitivity function of Patient 19 (T17M mutation), like the data from normal subjects, corresponded to that of the rod system, but was slightly reduced below the normal value. The function in Patient 16 (T58R mutation) resembled that of the cone system but was abnormally reduced by about 1.5 log units.<sup>28</sup>

A difference in peripheral retinal function in mutations T58R and T17M was detected with dark adaptometry (Fig. 8). The association of altitudinal field defects with prolonged rod adaptation in autosomal dominant retinitis pigmentosa<sup>18</sup> prompted us to study dark adaptation in these two mutations. Two-color dark adaptometry was performed in the three siblings (Patients 14 through 16) and their father (Patient 17) with the T58R mutation and Patient 19 with the T17M mutation at 36 degrees in the inferior field, a locus with normal or mildly impaired rod sensitivity in all of these patients. For comparison with the patients, the same test





**Fig. 5** (Jacobson and associates). Gray-scale maps of rod and cone sensitivity losses throughout the visual field of the right eyes of four of the patients whose kinetic fields are shown in Figures 3 and 4. Gray scales have 16 levels of gray, ranging from 0 to 54 dB for rods and 0 to 30 dB for cones; black indicates no detection of the stimulus.



**Fig. 6** (Jacobson and associates). Two-color dark-adapted static perimetric profiles along the horizontal meridian for the central 60 degrees. Top left, Normal subjects (mean data for ten subjects, aged 14 to 56 years). The dotted lines delimit 2 standard deviations above and below the mean. Middle and bottom left, Patients 3 and 4 with the Q344\* mutation. Top right, Patient 9 with the R135W mutation. Middle and bottom right, Patients 6 and 7 with the R135L mutation. Circles indicate 500 nm; arrowheads indicate 650 nm. For Patient 3, dotted lines delimit 2 standard deviations above and below the mean normal for 500 nm. For the other patients, the dotted lines delimit 2 standard deviations above and below the mean normal for 650 nm at the cone plateau ( $n = 5$ ; aged 29 to 54 years). The photoreceptor mediations for detection of the two colored stimuli are indicated in the graphs by the following letters: R, rods detect both; M, mixed (that is, rods detect 500 nm and cones detect 650 nm); C, cones detect both. Hatched bars represent the physiologic blind spot. N indicates nasal and T indicates temporal.

protocol was performed in four normal subjects.

In the normal subjects, recovery of sensitivity was complete in about 55 minutes after the light-adapting exposure (Fig. 8). A result from Patients 14 and 19 indicated that the recovery of sensitivity to levels before light adaptation was abnormally slow in both the T58R and the T17M mutations. However, there were substantial quantitative differences between the patterns of recovery displayed by the two families. In Patients 14 through 17 with the T58R mutation, the threshold elevation at 60 minutes after light adaptation was between 5 and 9 dB, whereas that in the patient with the T17M mutation was nearly 25 dB. Complete recovery of sensitivity occurred in about two hours in patients with the T58R mutation. In the patient with the T17M mutation, the slow recovery phase was much more prolonged, and full adaptation took almost 24 hours.

Another interesting feature of the adaptation

curve for the T58R mutation (Fig. 8) was that it reached the rod-cone break earlier than normal, even though there was no remarkable abnormality of cone thresholds. If the rod-cone break is defined as the time after light adaptation when the 500-nm stimulus is first detected by rods (that is, mixed rod and cone mediation, sensitivity difference between 500 and 650 nm  $\geq 13$  dB<sup>23</sup>) rather than cones, the values in the four normal subjects ranged between 14 and 16 minutes. Analysis of the dark-adaptation curves in the four family members with the T58R mutation showed that initial recovery was indeed faster than that in normal subjects, with their rod-cone break occurring between 8.5 and 11 minutes after light adaptation. The difference between these patients and the normal subjects was statistically significant (two-sample *t*-test,  $P = .0002$ ). No such abnormality was observed for the patient with the T17M, whose rod-cone break was at 14.5 minutes (within the normal range).



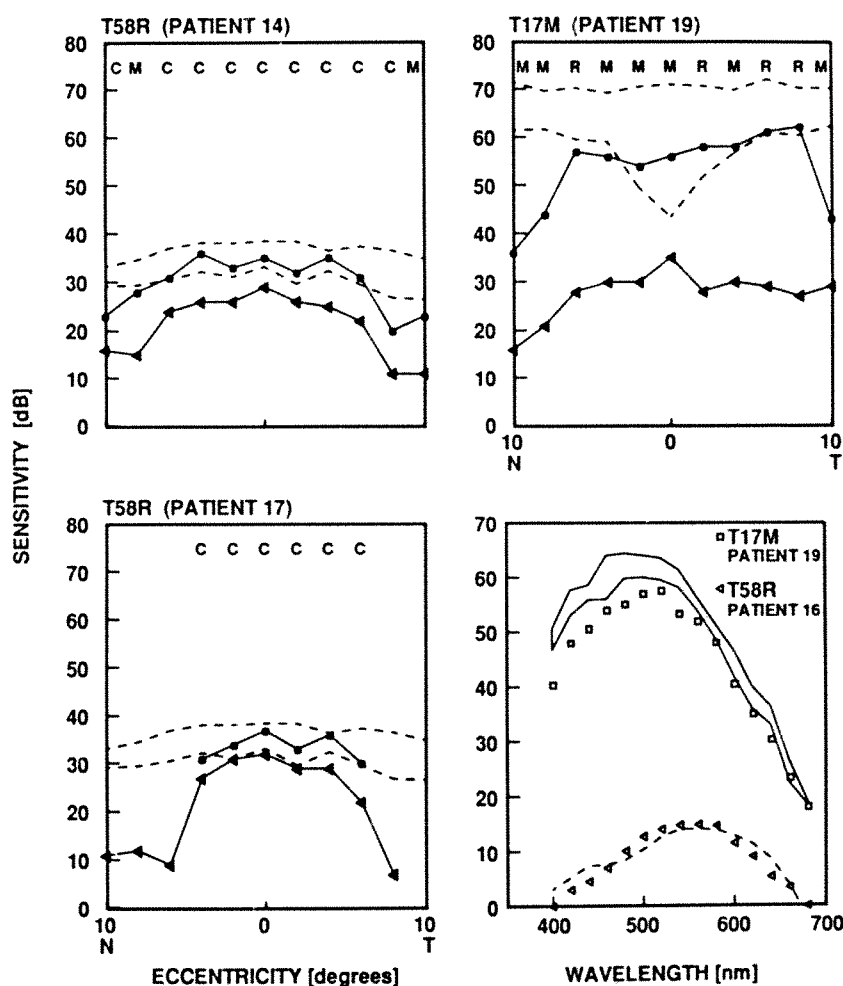
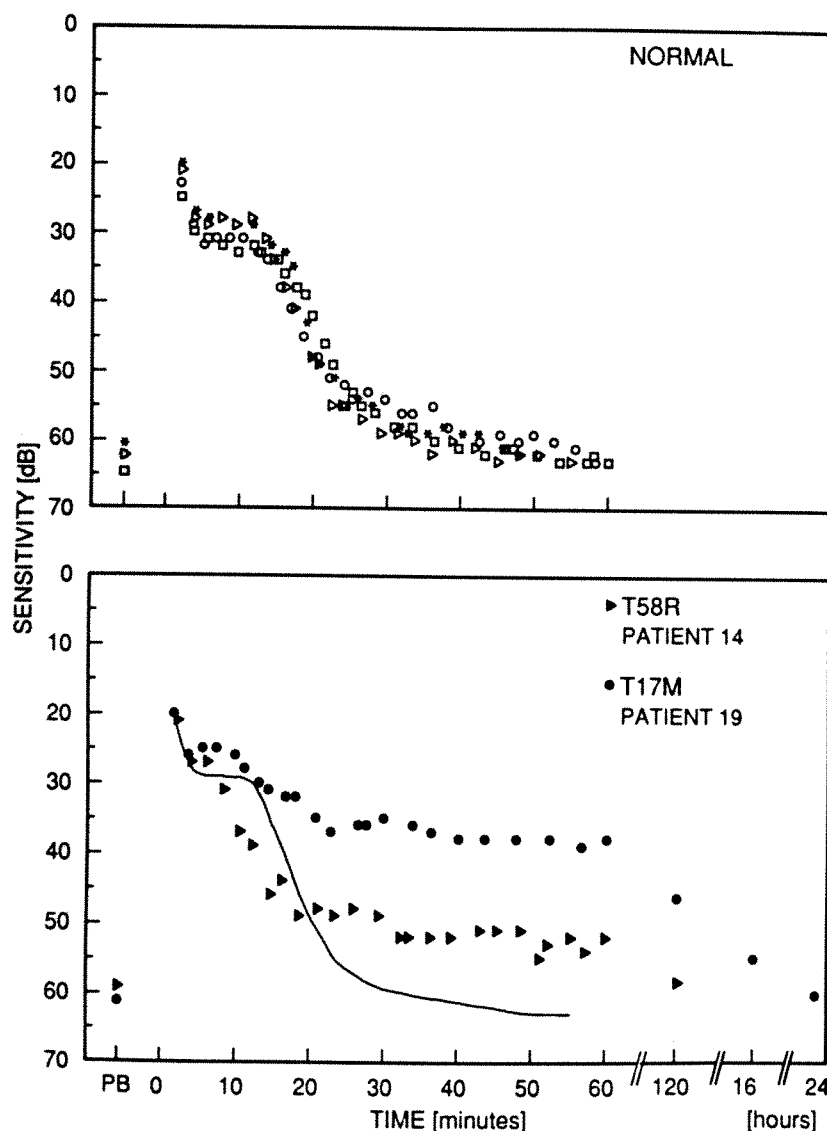


Fig. 7 (Jacobson and associates). Two-color dark-adapted profiles along the horizontal meridian for the central 20 degrees. Top and bottom left, Patients 14 and 17 with the T58R mutation. Top right, Patient 19 with the T17M mutation. Circles are 500 nm and arrowheads are 650 nm. Dotted lines delimit 2 standard deviations above and below the mean normal for 650 nm at the cone plateau in the graphs of Patients 14 and 17, and for 500 nm (dark-adapted) in the graph of Patient 19. Bottom right, Dark-adapted spectral sensitivity functions at 12 degrees in the inferior visual field in Patients 19 (unfilled squares) and 16 (unfilled arrowheads). Lines near the data of Patient 19 delimit the range of normal spectral sensitivity functions ( $n = 3$ ; aged 20 to 30 years). The dotted lines are a peripheral cone function that has been lowered to match approximately the data of Patient 16.

Visual pigment levels were measured with imaging fundus reflectometry in one or more representative patients carrying each of the five mutations. Figure 9 illustrates the difference spectra obtained from a region of the midperipheral retina in two members of the family with the Q344\* mutation, together with data obtained from the same location in a normal subject. Rhodopsin levels determined in these patients were substantially reduced from the normal level, even though rod sensitivities there were only mildly abnormal. In Patient 9 (with the R135W mutation), fundus reflectometry measurements in the midperipheral retina detected no rhodopsin. Similar results were obtained from the foveal and parafoveal region, where only cone pigments were detected. In Patient 12 (with the R135L mutation), measurements were carried out in the retinal region of best peripheral visual function (two-color dark-adapted static perimetry showed this to be cone mediated) and no rhodopsin could be detected.

The abnormal time courses of dark adapta-

tion exhibited by patients with the T58R and T17M mutations raised the possibility that the regeneration of rhodopsin might be abnormally prolonged. A modified procedure was therefore used for fundus reflectometry, in which exposure of the patient's eye to actinic light was minimized during alignment of the apparatus, and retinal reflectance data were obtained both before and immediately after the bleaching exposure. Changes in measured double density were thus obtained from the dark-adapted retina. Measurements designed to obtain rhodopsin regeneration data were then carried out during the time course after the bleaching. Double densities from the dark-adapted retina of Patient 15, the representative of the family with the T58R mutation, were reduced from normal double densities, barely exceeding the limits of reliable detectability (0.025 density units) anywhere within the measurement area. After the bleaching exposure, fundus reflectometry data were obtained for up to 45 minutes of dark adaptation, but no measurable



**Fig. 8** (Jacobson and associates). Dark adaptometry at 36 degrees in the inferior visual field with a 500-nm stimulus in normal subjects ( $n = 4$ ; aged 23 to 47 years) (top) and in Patients 14 (arrowheads) and 19 (circles) (bottom). The solid line represents data from a normal subject for comparison with the data of the patients. PB indicates prebleach measurement usually after at least three hours of dark adaptation and without previous light exposure.

pigment regeneration was evident during this time. A similar pattern of results was obtained from Patient 19 with the T17M mutation, with greatly reduced but detectable rhodopsin levels in some of the measurement area in the dark-adapted retina, but no recordable pigment regeneration within 40 minutes after a bleaching exposure.

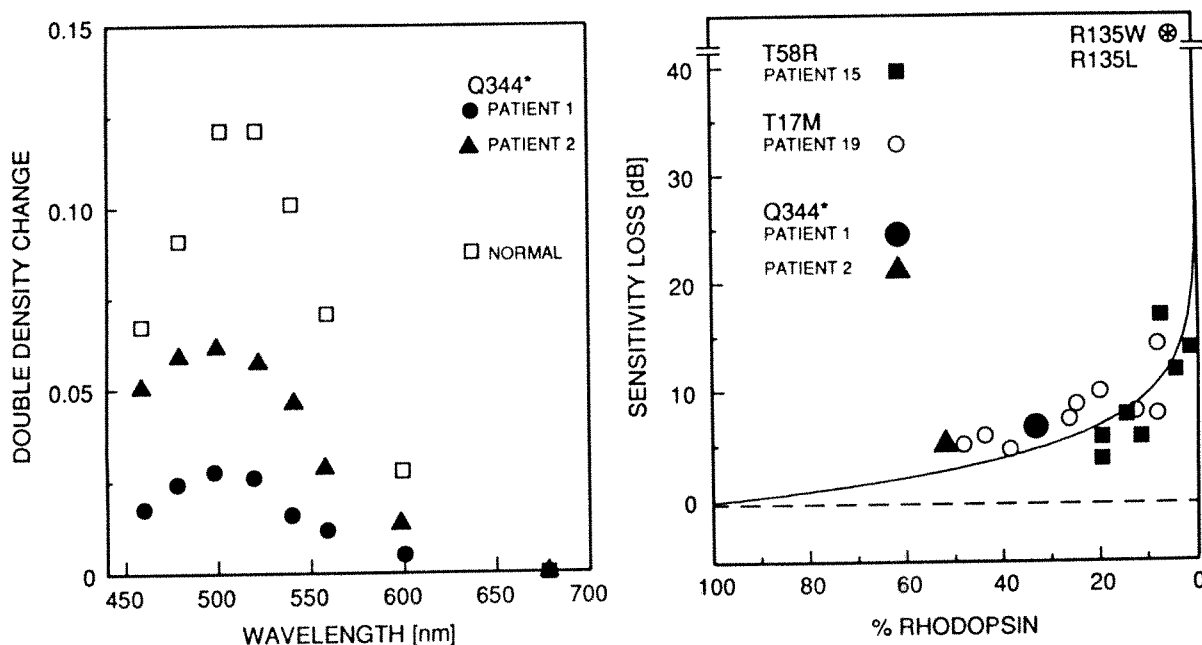
The relationship between the rod sensitivity losses and levels of rhodopsin measured in representative patients carrying the Q344\*, T58R, and T17M mutations are shown in Figure 9. Because the sensitivity losses and rhodopsin levels in the two patients with the Q344\* mutation showed little variation, the data for each of them are displayed as a single averaged value. Both the rod sensitivities and rhodopsin levels

were indeterminably low in both the R135W and R135L mutations. The solid line in Figure 9 is the curve that would be expected to define the relationship between reduced pigment levels in the rods and the sensitivity loss resulting from the consequent reduction in absorption of incident light.<sup>16</sup>

## Discussion

This study demonstrated differences in the patterns of rod and cone dysfunction in patients with different rhodopsin mutations. The retinal function test results from the younger or less severely affected patients we tested





**Fig. 9** (Jacobson and associates). Left, Double density difference spectra obtained from the midperipheral temporal retina of a normal subject (open squares) and Patients 1 (circles) and 2 (triangles) with the Q344\* mutation. The data were obtained after 30 minutes in darkness after a bleaching exposure that was expected to remove more than 95% of the rhodopsin originally present, and are the mean values obtained from a rectangular retinal area  $10 \times 10$  degrees, centered on 30 degrees along the horizontal meridian. Right, The relationship between the reduction of visual sensitivity and rhodopsin levels in Patients 1 (filled circle) and 2 (triangle) with the Q344\* mutation, Patient 15 (squares) with the T58R mutation, and Patient 19 (open circles) with the T17M mutation. Data from Patients 1 and 2 represent mean values for pigment levels and sensitivities for the central  $10 \times 10$ -degree rectangle of the measurement area. Data points from Patients 15 and 19 represent values obtained from individual locations within the measurement area. A notional point is included for the R135W (Patient 9) and R135L (Patient 12) mutations (circle enclosing asterisk) to indicate that both their rod sensitivity and rhodopsin levels were indeterminably low. Rod sensitivity loss was determined by subtracting patient data from mean results of normal subjects ( $n = 7$ ; aged 23 to 58 years) with the 500-nm target. The solid line represents the relationship that would be expected if the reduction in visual sensitivity was solely caused by the decreased probability of light absorption resulting from reduced levels of rhodopsin.

allowed us to define a phenotype for each of the mutations. Young patients carrying the Q344\* mutation had normal results of clinical examinations, full kinetic visual fields, slightly reduced rod but normal cone electroretinogram amplitudes, about 1 log unit of rod sensitivity loss but no cone sensitivity loss across the visual field determined perimetrically, and decreased rhodopsin levels as determined by fundus reflectometry. The more mildly affected patients with R135L and R135W mutations had ophthalmoscopic features of retinitis pigmentosa throughout their retinas, reduced kinetic fields to the  $I_{4e}$  target, undetectable rod and cone electroretinograms, no measurable rod sensitivity and only impaired cone sensitivity across the visual field, and no detectable rhodopsin. Patients carrying the T58R or T17M mutations appeared similar in phenotype by

having greater fundus pigmentary abnormalities in the inferior than superior retina, altitudinal kinetic fields, and sizable although abnormal rod and cone electroretinograms. Differences, however, were detectable with dark-adapted perimetry and dark adaptometry. Patients with the T58R mutation, unlike a patient with T17M mutation, had severe loss of rod sensitivity in a wide expanse of central retina, and the time course of rod adaptation was different in the two mutations, although both showed prolonged adaptation.

These functional phenotypes showed intrafamilial consistency in the sense that results in more severely affected members appeared to reflect a progression of the patterns in mildly affected members. In three families with substitutions at amino acid position 135, there was interfamilial consistency of phenotype. Recent

clinical studies of rhodopsin mutations P23H (proline-23-histidine) and P347L (proline-347-leucine) showed considerable clinical heterogeneity among patients with the same mutation, and the only distinguishing feature between patients with different mutations was the degree of severity.<sup>9-11,29</sup> Dark- and light-adapted static threshold perimetry, dark adaptometry, and fundus reflectometry, the techniques we used to elicit the differences between genotypes in this study, were not used in the studies of P23H and P347L.

The patterns of dysfunction in the R135L, R135W, T58R, and T17M mutations had some similarities to but also some differences from the functional phenotypes defined with the same techniques in earlier studies of families with autosomal dominant retinitis pigmentosa and unknown genotypes.<sup>12-18</sup> All members of the three families with mutations R135L and R135W showed loss of rod function diffusely across the visual field and some residual cone sensitivity, findings like those reported for the type 1 or diffuse form of dominant retinitis pigmentosa and unlike the type 2 or regionalized form which shows combined loss of rod and cone function in certain retinal regions and preservation of function in other regions.<sup>12-16</sup> Whereas patients with diffuse retinitis pigmentosa usually have substantially reduced or undetectable rod electroretinograms, but at least some cone signal,<sup>12,13,15,30</sup> our patients even at relatively young ages had undetectable rod and cone electroretinograms. The lack of measurable rhodopsin as determined by fundus reflectometry in our least-affected patients with Arg-135 mutations is in contrast to the previous finding in some patients with the diffuse phenotype of rhodopsin levels that were reduced but still relatively substantial in the presence of severe rod sensitivity loss.<sup>16</sup>

It is likely that the Arg-135 mutations are only two genotypes among many others in autosomal dominant retinitis pigmentosa that manifest severe rod dysfunction early in life and variably impaired cone function.<sup>12,31</sup> The recent finding that patients with other rhodopsin mutations may also show functional abnormalities resembling the diffuse phenotype<sup>32</sup> supports this conclusion.

In patients with autosomal dominant retinitis pigmentosa and altitudinal patterns of field loss, the later part of the rod-mediated branch of the recovery of sensitivity after extensive light adaptation can be abnormally slow.<sup>18</sup> This finding led us to study dark adaptation in pa-

tients with the T58R and T17M mutations. Our results, unlike those of previous reports,<sup>18,26</sup> indicated more than one type of abnormality in time course of adaptation. All tested members of the family with the T58R mutation showed an earlier than normal rod-cone break, a normal-appearing phase of increasing sensitivity to within 1.0 log unit of final sensitivity level, and then a slowing of a late phase of adaptation. The patient with the T17M mutation had a normal rod-cone break but drifted to the final sensitivity level over a much longer time course than did patients with the T58R mutation. Neither of these patterns is like that in mild systemic vitamin-A deficiency, which leads initially to a prolonged rod-cone break and then a slowing of later phases.<sup>33</sup> The lack of measurable levels of rhodopsin during the first 30 minutes or more of dark adaptation in the T58R and T17M mutations also differed from the pattern observed in vitamin A-deficient patients, who showed substantial rhodopsin regeneration during this period, when rod function was still absent. The functional abnormalities we found in patients with T58R and T17M mutations could be assessed in additional patients carrying these mutations, as such families have been found in other studies.<sup>3,6,8</sup>

The phenotype of the three young women from the family with the Q344\* mutation is, in our experience, rarely encountered in retinitis pigmentosa. Their examination was initially prompted by the finding that they carried the rhodopsin mutation but apparently lacked the disease<sup>5</sup>; they gave no history of night blindness or visual field loss and had normal results of eye examinations in the past. Our examination showed normal visual acuity and kinetic fields and no ophthalmoscopic abnormalities in all three siblings. The electroretinographic abnormalities, although relatively subtle, confirmed the disease in these patients.

The pattern of results with dark-adapted perimetry and fundus reflectometry in these young women with the Q344\* mutation differs from the diffuse and the regionalized phenotypes<sup>12,13,15,16</sup> by showing minimal rod sensitivity loss relatively uniformly across the visual field and a relationship of visual sensitivity and pigment levels that is consistent with decreased probabilities of quantal absorption by rhodopsin. It is also unusual in any type of retinitis pigmentosa to document a stage in the disease when cone function is normal. Visual acuity, cone electroretinogram amplitude, and cone perimetry were normal at a time when rod



function was abnormal. Although the advanced stage of this disease, as exemplified by Patients 4 and 5, was not distinguishable from other forms of retinitis pigmentosa with severe degrees of rod and cone dysfunction,<sup>24</sup> these older family members reported that they had excellent night and day vision in their youth. There are no further family members with intermediate stages of the disease, so the natural history of this retinal degeneration cannot be surmised at this time.

The rapidly expanding array of point mutations discovered in the rhodopsin gene in autosomal dominant retinitis pigmentosa clearly dictates that increasingly subtle criteria be used to try to distinguish phenotypic variations between them. Previously published classification schemes by phenotype for retinitis pigmentosa should probably be reserved now for those patients with unknown genotype. In the future, it will be important to try to relate the results of sophisticated phenotypic studies to those of more basic studies of the structure and function of mutant rhodopsins. In some instances functional abnormalities first disclosed by various test strategies in the patients may point to biochemical or physiologic abnormalities that can then be investigated in vitro.

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# B-scan Ultrasonography of Eyes Containing Intravitreal Gas

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Marc M. Whitacre, M.D.

Contact B-scan ultrasonography was performed on postoperative eyes containing intravitreal gas. Correlation of the ultrasonograms with the ophthalmoscopic findings disclosed that intraocular gas had a characteristic appearance on B-scan ultrasonography. Gas-fluid and gas-tissue interfaces were so highly reflective that no structures within or behind a bubble could be visualized. Shadowing, reverberation, and reflection artifacts were prominent, and dominated ultrasonographic findings. If the ultrasonographic characteristics of gas are understood, it is possible to use B-scan ultrasonography to determine if intraocular gas is present, whether there are one or several bubbles, and what percentage of the vitreous cavity is filled by gas. Specular reflection from a gas-fluid interface may be used to examine portions of the eye that might not otherwise be easily seen with ultrasonography.

**I**NTRAVITREAL GAS, which is used as an adjunct to complicated vitreoretinal surgery,<sup>1,2</sup> is gaining acceptance as a primary means of repairing uncomplicated rhegmatogenous retinal detachments.<sup>3</sup> Eyes that contain gas may develop a vitreous hemorrhage, cataract, hyphema, inflammatory membrane, or opacified cornea, which interfere with viewing the retina or vitreous cavity. In such cases B-scan ultrasonography may be used to provide information about the intraocular structures. Gas within

eyes generates unusual echoes that can be difficult to interpret. I studied these echoes in gas-containing postoperative eyes with clear media, and in vitro by using eye-bank eyes and table-tennis balls.

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## Material and Methods

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Contact B-scan ultrasonography was performed on the postoperative eyes of patients who underwent vitreoretinal surgery with intraocular gas injection. All eyes had clear media, allowing correlation of the ultrasonogram with the clinical examination. Water bath B-scan ultrasonography was also performed on eye-bank eyes that underwent simple gas injection or vitrectomy with gas-fluid exchange. Selected findings were duplicated on a table tennis ball that had a portion of its wall removed to create an acoustically clear window.

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## Results

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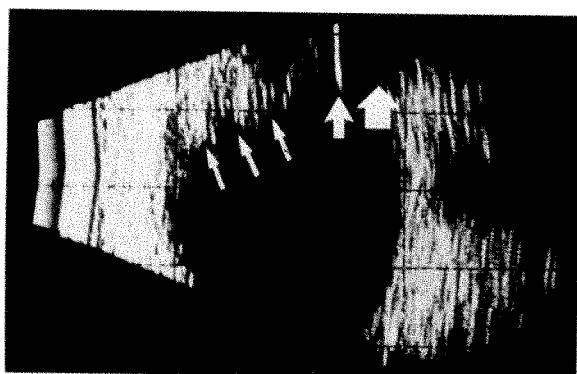
When a single intravitreal gas bubble was present, the echoes in the globe (Fig. 1) were the primary reflections from the gas-fluid (gas and vitreous) and gas-tissue (gas and lens) interfaces, reverberations between these interfaces, and reverberations between these interfaces and the ultrasound transducer.<sup>4</sup> The reverberation echoes arising from the gas-tissue and gas-fluid interfaces appeared as a diffusely echogenic zone beginning behind the gas-fluid and gas-tissue interfaces. These echoes had lower amplitudes than the primary echo from the surface of the gas-fluid or gas-tissue interface. Reducing the receiver gain eliminated the reverberation echoes and showed that a zone of profound shadowing was present behind the gas-fluid interface (Fig. 2). Reverberation echoes arising from ultrasound bouncing between

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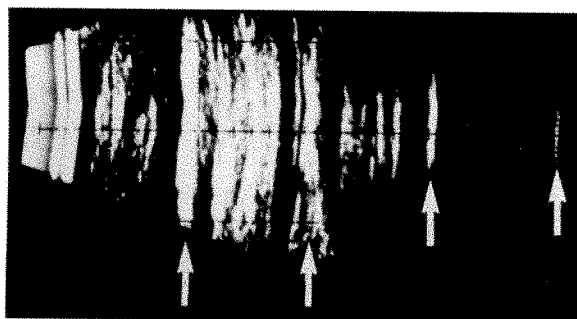


**Fig. 1 (Whitacre).** Ultrasonogram of an eye with a single intraocular gas bubble after pneumatic retinopexy. The ultrasound probe was in line with the visual axis and the top of the screen corresponds to the top of the patient's head. The patient's head was tilted slightly backward, bringing the bubble into contact with the lens. A trail of fine reverberations from the gas-fluid and gas-tissue interface (small arrows) and a single reverberation from the gas interface and the transducer tip (medium arrow) was seen at full receiver gain. The reverberation from the transducer tip was seen at twice the distance between the far left-hand side of the tracing and the anterior face of the gas bubble (the small arrow at the far left). Posterior shadowing was present (large arrow).

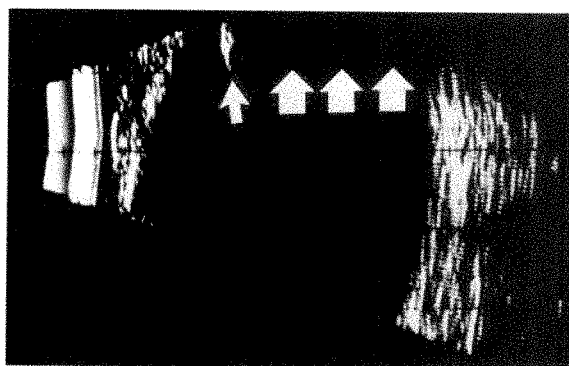
the gas-tissue or gas-fluid interface and the transducer tip occurred at harmonic intervals of the transducer-to-gas distance (Figs. 1 and 3).

Even small collections of bubbles 2 to 3 mm in diameter could be detected and identified (Fig. 4). A collection of small gas bubbles rarely created a comet tail artifact (Fig. 5).

When intraocular gas was present there was a

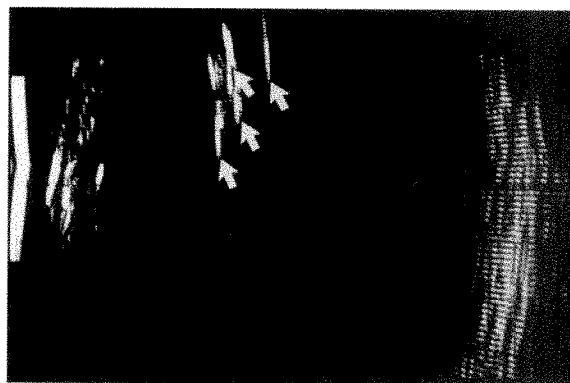


**Fig. 3 (Whitacre).** Ultrasonogram of an eye with a 60% gas-fill of the vitreous cavity. With the patient's face prone and the ultrasound probe in line with the visual axis, multiple reverberations (arrows) were produced by the ultrasound echoing between the gas-fluid interface and the transducer tip. Note the periodicity and diminishing amplitude of successive reverberations.



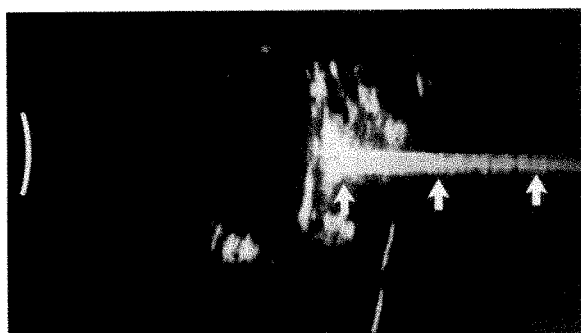
**Fig. 2 (Whitacre).** The head of the same patient was tilted slightly forward to displace the bubble posteriorly toward the superior equatorial region. The ultrasound probe was in line with the visual axis. When the receiver gain was reduced, only the primary echo of the gas-tissue interface was seen (medium arrow). The posterior shadowing has increased in extent (large arrows).

characteristic change in the ultrasonographic appearance of the eye as the patient's head position was varied. When the patient's head was erect, reverberations and shadowing dominated the superior portion of the eye occupied by and posterior to the gas bubble, though the inferior portion of the vitreous cavity could still be examined through the fluid it contained (Fig. 6). When the patient's head was face down, reverberations were prominent at the anterior edge of the bubble, and shadowing artifact was present behind that edge of the bubble (Fig. 7). In the face-down position the posterior vitreous cavity was totally obscured.



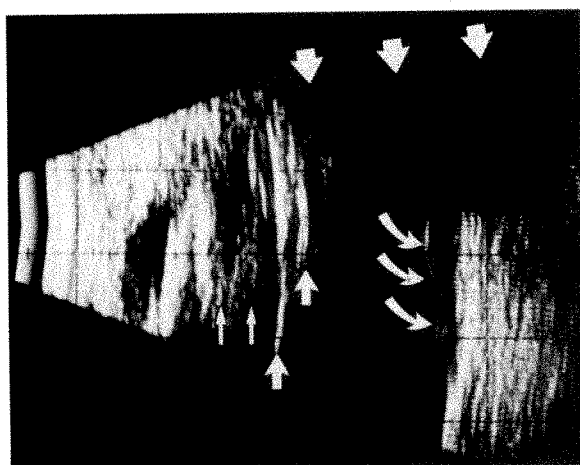
**Fig. 4 (Whitacre).** Immediately after pneumatic retinopexy multiple bubbles (resembling fish eggs) were present, which produced multiple echoes (arrows). The unequal spacing between the echoes proves that the echoes are not reverberations from a single source. The patient's head was erect and the ultrasound probe was in line with the visual axis.





**Fig. 5** (Whitacre). B-scan ultrasonogram of an eye-bank eye that had 0.2 ml of air injected intravitreally, forming multiple small bubbles. A comet tail artifact (arrows) was produced. The eye is horizontal and the probe was in line with the visual axis.

When 2 ml or more of gas was present within the eye a flat or nearly flat gas-fluid meniscus usually formed. Rather than being completely flat or slightly convex, the echoes produced by a meniscus were usually slightly concave and resembled a mound in profile (Figs. 7 and 8). The echoes were not entirely the result of vitreous debris floating at the gas-fluid interface, because they could be seen at the interface of water and air in a model eye. Unlike the other



**Fig. 6** (Whitacre). A 40% gas-fill of the vitreous cavity was present in an aphakic eye after vitrectomy. The patient's head was erect and the ultrasound probe was in line with the visual axis. Medium amplitude reverberations were present behind the iris from the gas-tissue and gas-fluid interface (small straight arrows). High amplitude reverberations were produced by ultrasound echoing between the gas surface and the transducer tip (medium straight arrows). Posterior shadowing was present (large arrows) and obscured the superior portion of a retinal detachment (curved arrows).

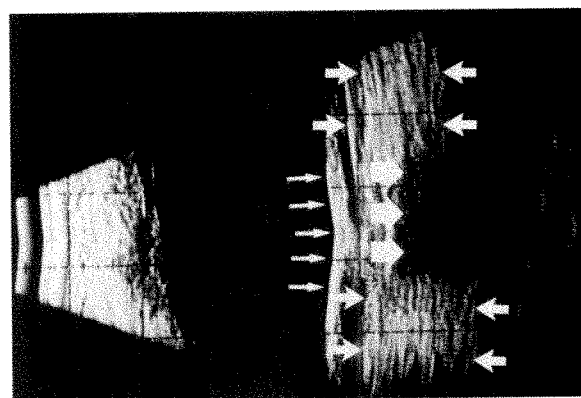
artifacts associated with intraocular gas, the appearance of this artifact varied slightly with the different B-scan ultrasound systems used.

When a smooth gas-fluid meniscus was present, specular reflection of ultrasound occurred. A clear reflection of the anterior segment of an aphakic eye is visible in Figure 9. Figure 10 is the ultrasonogram of an eye that developed hypotony two weeks after vitrectomy. A cyclitic membrane was easily seen on the mirror-image of the anterior segment. By varying the angle of incidence not only the anterior segment, but also the peripheral retina, could be visualized by using specular reflection off the gas-fluid interface.

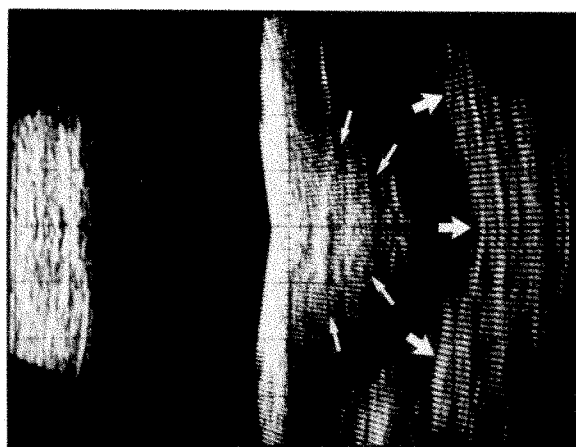
When globes were nearly filled with gas it was necessary to move the patient's head to a face-down position to demonstrate that intraocular fluid was present. Figures 11 and 12 show the ultrasonogram of an eye with an almost-total gas-fill. Figure 11 shows that when the probe was held parallel to the visual axis and the patient's head was erect, reverberation resulted because no intraocular fluid was in contact with the sclera adjacent to the probe, and no statement could be made about the fluid content of the eye. The small amount of fluid in the eye could be demonstrated with the head in the prone position (Fig. 12).

## Discussion

The reflection coefficient of ultrasound is the ratio of the amplitude of the reflected ultra-



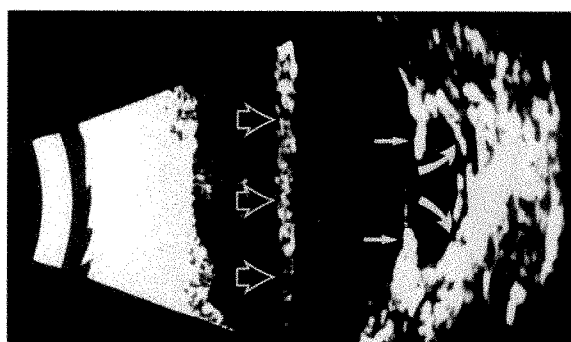
**Fig. 7** (Whitacre). When the patient's head was face down and the probe in line with the visual axis, the concave gas-fluid interface was clearly seen (fine arrows). Reverberations (medium arrows) and shadowing (large arrows) were present behind the gas-fluid interface.



**Fig. 8** (Whitacre). A mound artifact (fine arrows) in an aphakic eye containing a 50% gas-fill in the vitreous cavity. Posterior to the mound artifact were shadowing and reverberations (medium arrows). The face was prone and the probe in line with the visual axis.

sound pulse to the amplitude of the incident ultrasound pulse. The reflection coefficient is a function of the differences in the acoustic impedances at the interface of two materials. While the reflection coefficient varies between 0.1% and 7% for most normal ocular interfaces,<sup>5</sup> an intraocular gas-fluid or gas-tissue interface (regardless of the composition of the gas) has a reflection coefficient of 99.9%. This coefficient of reflection is so high that there is essentially no ultrasound transmission through the face of a gas bubble. Thus, structures behind the gas interface cannot be visualized<sup>4</sup> and any finding that appears behind a gas interface is an artifact. The supine head position commonly used for water bath ultrasonography is unsuitable for gas-containing eyes because even a small gas bubble would obscure most of the eye and orbital contents.

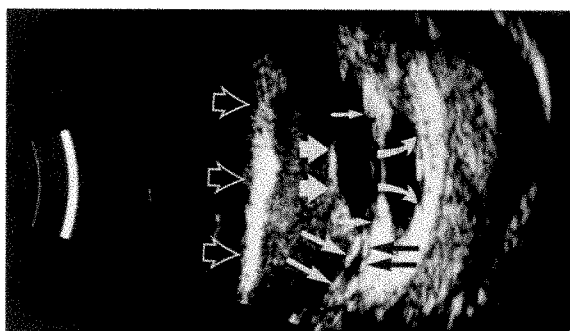
The prominent echo produced by the gas-fluid and gas-tissue interface can be used to estimate the intraocular gas content of an eye. If this method of estimating intraocular gas content is used, it is important to move the patient's head from an erect to a face-down position. The receiver gain should be reduced to see the echo produced by the meniscus clearly. An estimate of the intraocular gas content can be made by selecting a vector of the scan for analysis and estimating the gas-fill by using a formula relating the height of the bubble and the axial length of the eye to compute the volume of the gas bubble, as has been previous-



**Fig. 9** (Whitacre). Reflection of the anterior segment of an aphakic eye containing a 60% gas-fill of the vitreous cavity. The patient's face was in a prone position and the probe was in line with the visual axis. The mirror-image reflection of the iris (small arrows) and cornea (curved arrows) was clearly seen. Notice that these artifacts of reflection were more prominent than the gas-fluid meniscus (hollow arrows) that produced them.

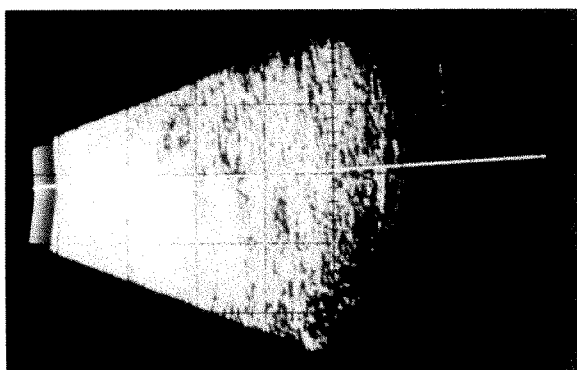
ly described with visual methods<sup>6</sup> or A-scan ultrasonography.<sup>7</sup>

The artifacts prominent in gas-containing eyes are shadowing, reverberation, and specular reflection. Shadowing always occurs behind a gas-fluid or gas-tissue interface. If the gas-fluid or gas-tissue interface is acoustically irregular, strong reverberations will be generated and may obscure the shadowing until the receiver gain is decreased. If a smooth meniscus is present at a gas-fluid interface, strong reverberations may not be generated and the profound



**Fig. 10** (Whitacre). Reflection of the anterior segment of a phakic eye with a 60% gas-fill of the vitreous cavity. The patient's face was in a prone position and the ultrasound probe was in line with the visual axis. The large hollow arrows point to the gas-fluid meniscus. The mirror-image reflections of the lens (large solid arrows), iris (small arrows), and cornea (curved arrows) were clearly seen, as were the cyclitic membranes bridging the space between the iris, lens, and ciliary body (medium white arrows and black arrows).



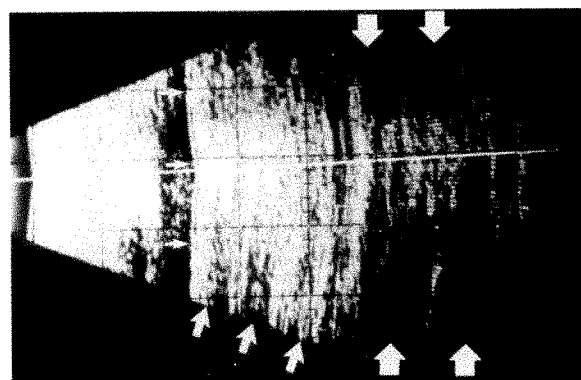


**Fig. 11** (Whitacre). An almost complete gas-fill is present after vitrectomy. When the patient's head was erect and the ultrasound probe was held in line with the visual axis, only the confluent reverberations of a gas-tissue interface were seen.

shadowing produced by gas may be prominent without any reduction in the receiver gain.

Reverberation is a train of one or more echoes generated when ultrasound is reflected between two surfaces. It occurs between irregular or multiple gas-fluid or gas-tissue interfaces. The numerous low to medium amplitude echoes behind a gas-fluid or gas-tissue interface are reverberations. At full receiver gain the reverberations fill in the anterior part of the shadowing produced by the gas. Reducing the gain makes the reverberations less apparent, and makes the primary echo of the gas interface and the posterior shadowing more prominent. Reverberations are most prominent at irregular gas-fluid interfaces (such as small bubbles or gas-tissue interfaces). This is because the ultrasound echoes between the irregular surfaces of the gas-fluid or gas-tissue interfaces. A comet tail artifact is a distinctive form of reverberation produced by ultrasound echoing between the gas-fluid interfaces of a cluster of bubbles.<sup>4,8-11</sup> Under some circumstances a smooth gas-fluid interface will produce an unusual mound-shaped reverberation.

Reverberations can also occur between the gas-fluid and gas-tissue interface and the ultrasound transducer tip. These reverberations are easily recognized by the equidistance and diminishing amplitudes of their successive echoes. One way to confirm that echoes are reverberation artifacts generated between the gas interface and transducer tip is to change the distance between the probe tip and the gas-tissue or gas-fluid interface. The distance between the probe tip and gas interface can be changed by increasing or decreasing the



**Fig. 12** (Whitacre). When the head was face down and the ultrasound probe parallel with the visual axis, the meniscus produced by a small amount of intraocular fluid was apparent as a well-formed echo (fine arrows). Reverberations (medium arrows) and shadowing (large arrows) were present behind the meniscus.

amount of gel coupling the probe tip to the eye. If the echoes are reverberations off the probe tip, the distance between each echo will change by an equal amount.

Whenever a smooth reflecting surface is present that is large as compared to the wavelength of the incident energy, specular reflections will occur. When specular reflection occurs from a gas interface, structures anterior or lateral to the meniscus will be projected behind the meniscus, and will be easily seen if the echoes fall within the region of shadowing. This phenomenon has been called mirror-image artifact.<sup>4,8,10,12</sup> This artifact is readily recognized when an eye containing a flat gas-fluid interface is examined with the patient's head in a face-down position. The mirror-image artifact is not merely an extraneous echo to be noted and ignored. It can be used to see detachments or membranes of the peripheral retina, choroid, or ciliary body that would be difficult to visualize by contact ultrasonography.

B-scan ultrasonograms are assumed to be point-for-point cross-sectional representations of the eye and orbit. This assumption is possible because of the relatively minor roles of reverberation, shadowing, and mirror-image artifacts. When an acoustically highly reflective substance such as gas is introduced into the eye or orbit, this assumption is no longer valid. Rather than being a subtle finding, these artifacts dominate the ultrasound image, and may completely obscure or falsely localize intraocular structures. These artifacts are not a meaningless collection of echoes, but an organized

mixture of signals that can yield information. Understanding these artifacts allows clinicians to modify their ultrasonographic examinations to exploit or minimize the artifacts produced by intraocular gas.

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### OPHTHALMIC MINIATURE

It sometimes occurred to No Ears that there might be a link between the fact that white people had weak eyes and the fact that they had little attachment to their true names. At the moment both mountain men were annoyed because they couldn't spot Martha's dog; if they couldn't see a dog merely because it had lain down to rest behind a bush a mile or two away, how would they see the truth in a person's name?

Larry McMurtry, *Buffalo Girls*  
New York, Simon & Schuster, 1990, p. 47



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# Anterior Chamber Aspirate Cultures After Uncomplicated Cataract Surgery

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James B. Dickey, M.D., Kenneth D. Thompson, Ph.D., and Walter M. Jay, M.D.

We cultured anterior chamber aspirates of 30 patients who had uncomplicated extracapsular cataract extraction or phacoemulsification. The aspirate was obtained at the time of wound closure. Of 30 patients, 13 (43%) had culture-positive anterior chamber aspirates. The total number of organisms recovered was 18, with three patients having multiple organisms identified. The most commonly isolated organisms were coagulase-negative *Staphylococcus* sp., occurring in eight of 18 isolates (44%). No eyes in our study developed endophthalmitis, even though almost one half had viable organisms growing from the anterior chamber aspirates. Inoculum sizes were extremely small (10 to 20 colony-forming units/ml). This study suggests that in humans, the anterior chamber is capable of clearing a low inoculum of bacteria after cataract surgery without the development of endophthalmitis.

IN 1972, Constantaras, Metzger, and Frenkel<sup>1</sup> concluded that the anterior chamber remained sterile after intracapsular cataract surgery. More recently, Sherwood and associates<sup>2</sup> suggested that fluid from the conjunctival sac, contaminated with bacteria, routinely enters the anterior chamber during extracapsular cataract extraction. Sherwood and associates<sup>2</sup> found a 29% bacterial contamination rate of the anterior chamber after extracapsular cataract extraction. They did not, however, determine the

specific organisms or inoculum sizes within the anterior chamber.

In this study, we cultured fluid from the anterior chamber of 30 patients who had undergone uncomplicated extracapsular cataract extraction or phacoemulsification. This study was designed to allow for quantification of organisms, and to assess relative frequencies of species cultured from the anterior chamber at the conclusion of cataract surgery.

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## Patients and Methods

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We studied 30 patients who met the following inclusion criteria: (1) no history or objective evidence of previous surgery or penetrating injury to the eye; (2) no local or systemic infection at the time of surgery; (3) no evidence of posterior lens-capsule rupture at the time of surgery; and (4) no additional procedures combined with the uncomplicated cataract extraction, except for intraocular lens implantation.

Patients were hospitalized at the Hines Veterans Administration Hospital the day before surgery and their eyelashes were trimmed at the bedside. Each patient received a 4% chlorhexidine gluconate facial scrub and two drops of gentamicin ophthalmic solution into the eye on the night before surgery. The eyes were dilated with 1.0% cyclopentolate, 2.5% phenylephrine, and 0.03% flurbiprofen drops before surgery. All medications used before surgery were sterile. In the operating room, percutaneous van Lint and retrobulbar blocks were given. To lower intraocular pressure, a compressive device was placed over the eye for five minutes. One drop of 0.5% tetracaine hydrochloride was then instilled into each eye, and aseptic preparation was performed on all of the patients in an identical fashion. The eyelids, nose, cheek, eyebrow, and forehead were scrubbed with 0.25% hexachlorophene in concentric rings outward from the eye for a duration of four minutes. Careful attention was given to the eyelash bases

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and eyelid margins, which were scrubbed with a cotton-tipped applicator. The eye and surrounding skin were then irrigated with sterile 0.9% saline solution. Irrigation was succeeded by repeating the scrubbing measures previously outlined with substitution of 5% povidone-iodine for hexachlorophene. One drop of povidone-iodine was placed onto the cornea and allowed to work its way into the fornices. Excess povidone-iodine was then gently blotted from the skin without further irrigation.

The head was draped with sterile cloth towels in the manner described by King and Wadsworth.<sup>3</sup> A sterile linen drape was placed over the patient, exposing only the eye for surgery. Clear self-adhesive plastic was placed over the eyelids, exposing the eyelashes and eyelid margins. Uncomplicated cataract extraction was then performed by an extracapsular technique (22 cases) or via phacoemulsification (eight cases). A posterior chamber intraocular lens was placed in all but one eye (this patient was aphakic in the fellow eye and preferred aphakic spectacles). All surgeries were performed using a fornix-based conjunctival flap. In addition to surgical instruments, sterile balanced salt solution with epinephrine, 1:10,000 dilution; and sterile sodium hyaluronate and acetylcholine were placed into the anterior chamber during surgery. The viscoelastic was removed before acetylcholine injection. At the end of the operation, before final corneoscleral suture placement, a sterile 27-gauge cannula attached to a tuberculin syringe was placed into the anterior chamber through the surgical wound. Fluid (0.1 to 0.2 ml) was then aspirated from the anterior chamber. Subconjunctival gentamicin was injected into the inferior fornix at the conclusion of every operation.

One of us (J.B.D.) then immediately inoculated equal portions of the aspirated fluid onto a chocolate agar plate and into a thioglycolate broth tube. The culture plates were sealed in the operating room and transported by automobile from the Hines Veterans Administration Hospital to the Loyola University Medical Center Clinical Microbiology Laboratory (approximate distance, 500 yards). Cultures were incubated at 37 C with 5% carbon dioxide, and held for two weeks to allow fungus and anaerobe growth. Both media (thioglycolate broth and chocolate agar) were chosen because of their nonselective nature. The chocolate agar allowed quantification of organisms into colony-forming units, whereas the broth allowed only qualitative organism identification. Cul-

tures were interpreted by experienced laboratory personnel using accepted techniques.<sup>4</sup> Cultures were called positive only if organisms grew in the central inoculated areas of the agar within four days of inoculation. The time requirement, however, was not applied to fungus and *Propionibacterium* sp. because they grow at a much slower rate.<sup>4</sup>

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## Results

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Of 30 eyes, 13 (43%) had positive anterior chamber aspirate cultures (Table 1). Three patients had multiple organisms recovered from their anterior chamber aspirate. The total number of isolates from these 13 patients was 18. Of the 18 isolates, 15 were found on chocolate agar and three were identified from turbid thioglycolate broth (Table 2). The most commonly isolated organisms were *Staphylococcus coagulase-negative* organisms, occurring in eight of 18 isolates (44%). *Corynebacterium* sp. were the second most frequently found organisms (four of 18, 22% of all isolates). One of each of the following species was isolated: *S. aureus*, presumed Group-D *Streptococcus* sp., *Bacillus* sp., *Propionibacterium* sp., *Moraxella* sp., and *Alter-naria* sp.

Use of the chocolate agar allowed the quantification of organisms into colony-forming units (Table 1). The inoculum dose of organisms was found to be quite small. Most organisms were found in inoculum sizes of ten to 20 colony-forming units/ml. The broth could not be used as a measure of quantification, but only for qualitative purposes (Table 2).

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## Discussion

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This study documents the presence of viable organisms in the anterior chamber of patients after uncomplicated cataract surgery. Endophthalmitis did not develop. Our results differ from those of Constantaras, Metzger, and Frenkel.<sup>1</sup> Their study was performed after intracapsular cataract extraction without intraocular lens implantation, and demonstrated one positive anterior chamber aspirate culture out of 100 eyes. This one culture grew *S. epidermidis* and was considered a contaminant. It was the conclusion of this previous study that the aqueous humor remained sterile throughout routine cataract extraction.



TABLE 1  
STUDY PATIENTS WITH POSITIVE CULTURES

PATIENT NO.	STUDY DAY	ORGANISM	COLONY-FORMING UNITS/ML	INTERVAL TO GROWTH (DAYS)
3	3	Coagulase-negative <i>Staphylococcus</i> sp.	90	3
4	10	Coagulase-negative <i>Staphylococcus</i> sp.	10	4
		<i>Corynebacterium</i> sp.	10	4
6	13	Coagulase-negative <i>Staphylococcus</i> sp.	20	3
		<i>Corynebacterium</i> sp.	20	3
		<i>Moraxella</i> sp.	20	3
7	15	Coagulase-negative <i>Staphylococcus</i> sp.	20	3
13	27	Coagulase-negative <i>Staphylococcus</i> sp.	20	2
14	27	Coagulase-negative <i>Staphylococcus</i> sp.	11	2
15	27	<i>Bacillus</i> sp.	16	2
19	31	<i>Alternaria</i> sp.	16	13
		Group-D <i>Streptococcus</i> sp.	Broth	3
		<i>S. aureus</i>	Broth	3
20	34	<i>Corynebacterium</i> sp.	10	3
21	36	Coagulase-negative <i>Staphylococcus</i> sp.	13	3
23	38	Coagulase-negative <i>Staphylococcus</i> sp.	17	1
29	50	<i>Propionibacterium</i> sp.	Broth	7
30	50	<i>Corynebacterium</i> sp.	14	2

A comparison of the method used in our study and that used by Constantaras, Metzger, and Frenkel<sup>1</sup> may help explain the difference in results. Both studies used a solid blood agar and a broth. In the study by Constantaras, Metzger, and Frenkel, intracapsular surgery was performed using a corneoscleral limbus-based conjunctival flap. This type of approach could allow for a less direct path of entry for organisms into the anterior chamber from the ocular adnexa than would the fornix-based conjunctival flaps used in our study. However, the more important difference in findings probably

relates to the small inoculum doses of organisms in the anterior chamber fluid. Most isolates were between ten and 20 colony-forming units/ml in our study. Because our study included only cases with an intact posterior capsule, we were able to aspirate up to 0.20 ml of fluid to facilitate organism recovery. Constantaras, Metzger, and Frenkel<sup>1</sup> based their conclusions on one drop of anterior chamber aspirate per patient.

Sherwood and associates<sup>2</sup> demonstrated that fluid on the external ocular surface entered the anterior chamber during extracapsular cataract

TABLE 2  
SPECIES OF ORGANISMS ISOLATED AND FRACTION OF TOTAL ISOLATES

ORGANISM	THIOGLYCOLATE BROTH	CHOCOLATE (BLOOD) AGAR	TOTAL ISOLATES (N = 18) (%)
Coagulase-negative <i>Staphylococcus</i> sp.	0	8	8 (44)
<i>Corynebacterium</i> sp.	0	4	4 (22)
<i>S. aureus</i>	1	0	1 (6)
Group-D <i>Streptococcus</i> sp.	1	0	1 (6)
<i>Bacillus</i> sp.	0	1	1 (6)
<i>Propionibacterium</i> sp.	1	0	1 (6)
<i>Moraxella</i> sp.	0	1	1 (6)
<i>Alternaria</i> sp.	0	1	1 (6)

surgery. Of 101 patients who underwent extracapsular cataract extraction, 29 had organisms recoverable from their anterior chamber fluid at the conclusion of the cataract surgery. Ninety of these same patients had organism growth from postoperative conjunctival drain samples. Sherwood and associates,<sup>2</sup> however, did not delineate the organism species, or the frequencies with which the species were recovered from anterior chamber aspirates. Rather, the anterior chamber fluid isolates were grouped indistinguishably with isolates from the external ocular drain in their final analysis. Furthermore, the microbiologic techniques used by Sherwood and associates<sup>2</sup> allowed only qualitative organism identification and not quantification into actual numbers of viable organisms.

Our results are consistent with previous studies that document the presence of organisms capable of causing endophthalmitis on the cataract operative field.<sup>5-10</sup> One preoperative preparation technique by Apt and associates<sup>10</sup> showed that the use of Neosporin eyedrops, three times per day, for three days before surgery, in addition to a standardized povidone-iodine scrub could decrease the bacterial count of the conjunctiva by 99.5%, but failed to achieve absolute sterility in over 50% of the patients. Although we did not strictly adhere to the technique described by Apt and associates,<sup>10</sup> we did perform a similar periocular facial scrub. When we compared the organisms and frequencies that Apt and associates found on conjunctival culture after their preoperative preparation to the organisms cultured from the anterior chamber of eyes and their frequencies, the results were similar.<sup>10</sup>

Numerous investigators from other surgical disciplines have documented a substantial rate of bacterial contamination in many types of surgical wounds.<sup>11-15</sup> Organisms gaining entrance into surgical wounds are predominantly those same organisms that constitute common skin flora (coagulase-negative *Staphylococcus* sp., *Propionibacterium* sp., and other diphtheroids).

*Staphylococcus epidermidis* (a coagulase-negative *Staphylococcus* sp.) is recognized as the leading cause of endophthalmitis after cataract surgery, with *S. aureus*, gram-negative rods, and *Streptococcus* sp. constituting most of the remainder of the causes.<sup>16-18</sup> The frequency of coagulase-negative *Staphylococcus* sp. as a percentage of total isolates in our study (44%, or eight of 18 eyes) was similar to the incidence that this organism has as a cause of culture-positive endophthalmitis after cataract extraction (38% to 60%).<sup>16,17</sup>

The eyes with anterior chamber aspirates positive for microorganisms did not develop endophthalmitis in our study. We believe that organism virulence, inoculum size, and the integrity of the posterior lens capsule are factors that influence the progression or nonprogression to endophthalmitis. Also, we suggest that the aqueous humor possesses antimicrobial properties. Immunoglobulins<sup>19</sup> and complement components<sup>20</sup> have been demonstrated in the aqueous humor of patients undergoing cataract surgery. Mechanical filtration through the trabecular meshwork may also reduce the intraocular bacterial load.<sup>21</sup>

Organisms of higher virulence cause endophthalmitis at a rate higher than that cultured in our anterior chamber aspirates. *Staphylococcus aureus* is found to be a cause of endophthalmitis with a much higher frequency (21% to 26%)<sup>16,17</sup> than its presence in the anterior chamber would predict. Conversely, *Corynebacterium* sp. and other diphtheroids seed into the anterior chamber with a much higher frequency than they are a cause for infection (0% to 1%).<sup>16,17</sup> The diphtheroid group has long been identified as an organism of low virulence that rarely causes ocular infection.<sup>22</sup>

Animal studies confirm the importance of organism virulence by demonstrating a direct relationship between organism virulence and inoculum size needed to induce endophthalmitis.<sup>23,24</sup> These studies also demonstrate a greater ability the anterior chamber has to clear itself of organisms than has the vitreous humor. Many more organisms must be injected into the anterior chamber to induce endophthalmitis than are needed by vitreous injection.<sup>23,24</sup> In humans, also, the anterior chamber appears to clear itself of organisms better than does the vitreous humor. Anterior chamber paracentesis cultures may be negative in cases of endophthalmitis in which the vitreous humor is positive for organisms.<sup>18,25,26</sup>

Preservation of the posterior capsule augments the anterior chamber's ability for sterilization by forming a barrier to prevent organisms from seeding into the vitreous humor.<sup>27-29</sup> Beyer and associates<sup>27</sup> observed that injection of greater than 10,000 colony-forming units of *S. aureus* into the anterior chamber was necessary to induce endophthalmitis in primates when the posterior capsule was intact. Similarly, Records and Iwen<sup>29</sup> found that injection into the anterior chamber of approximately 1,000 colony-forming units of *S. aureus* was necessary to induce endophthalmitis in normal rabbit eyes, and in rabbit eyes after extracapsular lens extraction with posterior capsule preservation,



compared to only 14 colony-forming units in similar eyes if the posterior capsule had been incised. The anterior chamber inoculum sizes we observed in our study were quite small in comparison to those needed to induce endophthalmitis in animals with an intact posterior capsule.

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# Lens Capsule and Epithelium in Age-related Cataract

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and Joseph Horwitz, Ph.D.

On the basis of preoperative assessment of patient characteristics, intraoperative obtainment of a lens-capsule and epithelium specimen, histopathologic investigation of lens capsule and epithelium, and biochemical analysis of glutathione reductase in lens epithelium, age-related cataract was studied in 50 adult patients who underwent consecutive extracapsular cataract-posterior chamber lens implant surgery. Patients (25 men and 25 women; age range, 41 to 91 years; mean age, 75 years) had a wide range of systemic and ocular disease; 17 of 50 (34%) patients had a history of severe vision-impairing cataract in a first-degree relative. Anterior lens-capsule thickness ranged from 10 to 22  $\mu\text{m}$ , with a mean of 17  $\mu\text{m}$ . Statistical analysis of lens-epithelium ultrastructure in 41 of 50 specimens documented mixing of normal and abnormal cells, verified a gradation in the degree of abnormal ultrastructural features, and demonstrated a statistically significant decrease in epithelial cytologic activity with advancing age ( $P = .038$ ). Biochemical analysis documented a severe glutathione reductase deficiency in nine of 39 (23%) lens-epithelium specimens, possibly reflecting a dietary deficiency of riboflavin.

**C**ATARACT IS THE cause of blindness in approximately 17 million of the estimated 42 million (40.2%) blind persons throughout the world.<sup>1,2</sup> Factors associated with the onset or progression of cataract include genetic considerations; met-

abolic diseases; nutritional disorders; drug treatment; ionizing radiation; exposure to ultraviolet, visible, and infrared light; and trauma.<sup>3,4</sup> Although many intrinsic (genetic) and extrinsic (host-related and environmental) factors may contribute to cataract, increasing age is most strongly and consistently associated with the prevalence of cataract.<sup>5</sup> Therefore, for cataract development without specific cause in adult patients, age-related cataract is the appropriate diagnosis.

Consistent with its worldwide importance, numerous studies of age-related cataract have focused on epidemiologic factors, medical and surgical management, histologic findings,<sup>6,8</sup> and biochemical analysis.<sup>5,9</sup> Therefore, we studied a series of patients undergoing cataract surgery by assessment of clinical characteristics before surgery, by obtainment of a lens-capsule and epithelium specimen during surgery, by histopathologic investigation of lens capsule and epithelium, and by biochemical analysis of glutathione reductase concentration in lens epithelium.

Glutathione reductase, which requires flavin adenine dinucleotide for its function, is a catalyst for regeneration of reduced glutathione and therefore has an important role in the biologic defense against oxidative damage.<sup>9,10</sup>

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## Patients and Methods

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The patients were 50 adults with age-related cataract who had consecutive cataract surgery with lens-capsule and epithelium specimen obtainment during the study period. In the one patient who had bilateral cataract surgery, one eye was randomly chosen for a total of 50 eyes.

Additionally, ten adults who had cataract surgery, and in whom lens-capsule and epithelium specimens were obtained, were studied by means of scanning electron microscopy.

Before surgery, cataract surgery patients had a general physical examination and a multifactorial medical history was taken. Complete

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ophthalmic history and examination included quantitative assessment of the lens capsule, anterior and posterior subcapsular areas, five sectors of lens cortex, and lens nucleus; and cataract photography with diffuse illumination, standardized slit-lamp procedures, and polarized retroillumination techniques.<sup>5</sup>

At surgery, which consisted of an extracapsular cataract extraction-posterior chamber intraocular lens procedure in all patients, anterior capsulotomy was performed by continuous-curve capsulorhexis or by use of multiple-puncture circumferential capsulotomy technique. The central 5 to 6 mm of anterior lens capsule and adherent lens epithelium were withdrawn with forceps and delivered directly to the laboratory for histopathologic and biochemical studies.

Specimens were managed according to a protocol designed to optimize preservation of biochemical and ultrastructural status of the surgical specimen. Immediately after surgical removal, the tissue specimen was suspended in isotonic balanced salt solution. Any cortical fibers or erythrocytes were removed and the specimens were processed as a whole mount for scanning electron microscopy or divided into equivalent samples for histopathologic study or biochemical analysis.

*Histopathologic findings*—Histopathologic findings were evaluated by use of scanning electron microscopy, light microscopy, and transmission electron microscopy.

For scanning electron microscopy, tissue was fixed as a whole mount for one hour at 4°C in an isotonic 2.5% glutaraldehyde, 2% formaldehyde fixative in sodium phosphate buffer (pH, 7.3), postfixed with 1.0% osmium tetroxide, dehydrated in ethanol, critical-point dried, sputter-coated with gold, and viewed with a scanning electron microscope.

For light and transmission electron microscopy, tissue samples were obtained from the central portion of the bisected capsulotomy specimen as a strip that measured approximately 1 × 5 or 1 × 6 mm. The sample included the anterior pole and corresponded to the sample used for biochemical analysis. The tissue was fixed according to the previously described protocol, dehydrated in ethanol, and embedded in epoxy.

For light microscopy, 1- $\mu$ m sections were stained with toluidine blue before examination and photomicrography. Orientation of the plane of sectioning was maintained perpendicular to the anterior surface of the lens to repre-

sent capsule and epithelium characteristics and dimensions accurately.

For transmission electron microscopy, ultrathin sections of 80 to 100 nm were cut with a diamond knife on an ultramicrotome. Sections were collected on film on copper single-hole grids and counterstained with uranyl acetate and lead acetate before examination with an electron microscope.

Lens-capsule thickness of sections studied by light microscopy was measured with a calibrated reticule in the light-microscope eyepiece. Epithelial cell diameter (as nucleus-to-nucleus distance) was measured by contiguous cell profiles in thin sections. The basal surface of the lens epithelium was continuous with the lens capsule.

The ultrastructure of the lens epithelium was assessed by transmission electron microscopy. Epithelial cells with a central section of the nucleus in the cell profile were selected at uniform intervals along the full length of the specimen to ensure a representative sample and to provide for a detailed study of a representative number of cells. Ultrastructural features were assigned graded scores to represent their quantity and condition. The mean score for each ultrastructural feature in the representative cells of the sample was used for statistical analysis. Ultrastructural features studied and scored in this manner included endoplasmic reticulum, Golgi apparatus, mitochondria, nucleus, lysosomal bodies, and extracellular lacunae.

*Biochemical analysis*—For biochemical analysis, tissue samples were obtained from the capsulotomy specimen. These samples were equivalent to the samples used for histopathologic study.

Glutathione reductase activity in the lens epithelium was measured by use of a modified enzyme-recycling technique.<sup>11</sup> The sample was suspended in 160  $\mu$ l of 50 mM phosphate-buffered potassium solution (pH, 7.0) containing 2 mM ethylenediaminetetra-acetic acid, sonicated at low power over ice, and centrifuged at 15,000 rpm for 15 minutes. The supernatant was used for the enzyme analysis and the pellets were discarded. The reaction mixture contained 510  $\mu$ l of the previously described buffer, 70  $\mu$ l of the sample, 40  $\mu$ l of 0.2 M oxidized glutathione, and 30  $\mu$ l of 2.2 M reduced nicotinamide adenine dinucleotide phosphate. The reference mixture replaced buffer for the sample. After incubation at 37°C for 30 minutes, 50  $\mu$ l of 63.1 mM 5'-5'-dithio-

bis-2-nitrobenzoic acid was added to each cuvette and the reaction was monitored spectroscopically at 412 nm on a spectrophotometer. Glutathione reduced by glutathione reductase was complexed with nitrobenzoic acid and the absorbance of the colored product was measured at 412 nm.

Glutathione reductase activity was measured with and without the addition of supplemental flavin adenine dinucleotide. The ratio of the activity with supplement added to the reaction divided by the glutathione reductase activity without supplement is defined as the glutathione reductase activation coefficient. This coefficient is useful for comparison among patients and as a possible indicator of riboflavin deficiency.

Glutathione reductase deficiency in lens-epithelium samples was indicated by one of the following conditions: (1) when there was no glutathione reductase activity with or without supplement, (2) when there was glutathione reductase activity only with supplement, or (3) when the glutathione reductase activation coefficient was equal to or greater than 1.25.

All data, including patient characteristics, cataract surgery information, histopathologic study, and biochemical analysis, were analyzed by means of the Statistical Analysis System (SAS Institute, Inc., Cary, North Carolina).

## Results

The 50 patients with age-related cataracts consisted of 25 men and 25 women ranging in age from 41 to 91 years and a median age of 75 years (Table 1). The patients had a wide range of systemic disease and a number of potentially relevant conditions during the five years before cataract surgery. Hypertensive cardiovascular

disease in 22 of 50 patients (44%), arthritis in six of 50 patients (12%), peptic ulcer in three of 50 patients (6%), diabetes mellitus in two of 50 patients (4%), and metastatic carcinoma in one of 50 patients (2%) occurred. Systemic medications considered to be possibly cataractogenic<sup>12</sup> and received by patients on a regular basis for three months or more during the five years before cataract surgery were recorded (Table 2). Seventeen of 50 patients (34%) had a family history of cataract that severely decreased vision in one or more first-degree members (seven in parents, six in siblings, and four in parents and siblings).

Ophthalmic history and examination indicated cataract-related vision impairment that interfered with important activities in every one of the 50 patients. Before surgery, the corrected visual acuity of the 50 patients ranged from 20/30 (in a patient with impaired reading and glare disability) to counting fingers at 1 foot (Table 3). Previous disorders in the surgical eyes are also recorded (Table 4).

Extracapsular cataract extraction with posterior chamber intraocular lens implantation was performed in 50 of the 50 eyes (100%). Anterior capsulotomy was performed by use of continuous-curve capsulorhexis or multiple-puncture circumferential capsulation technique. Every operation was completed in accordance with the preoperative plan.

*Scanning electron microscopy*—Whole mounts of capsulotomy specimens, processed for scanning electron microscopy and drawn to scale, showed the smooth edge of the continuous-curve capsulotomy (Fig. 1) and the sharply serrated, picket-fence edge of the multiple-puncture capsulotomy (Fig. 2). By use of scanning electron microscopy, the smooth edge of the continuous-curve capsulotomy, which was elastic and resistant to tearing, was visible (Fig. 3). In contrast, the multiple-puncture capsu-

TABLE 1  
PATIENT AGE AND GENDER

AGE (YRS)	MEN	WOMEN	TOTAL
40-49	1	1	2
50-59	2	0	2
60-69	4	8	12
70-79	13	8	21
80-89	5	7	12
90+	0	1	1
Total	25	25	50

TABLE 2  
POSSIBLE CATARACTOGENIC SYSTEMIC MEDICATIONS

MEDICATION	PATIENTS	
	NO.	%
Corticosteroids, systemic	3	6
Naproxen	2	4
Ibuprofen	1	2
Colchicine	1	2
Allopurinol	1	2



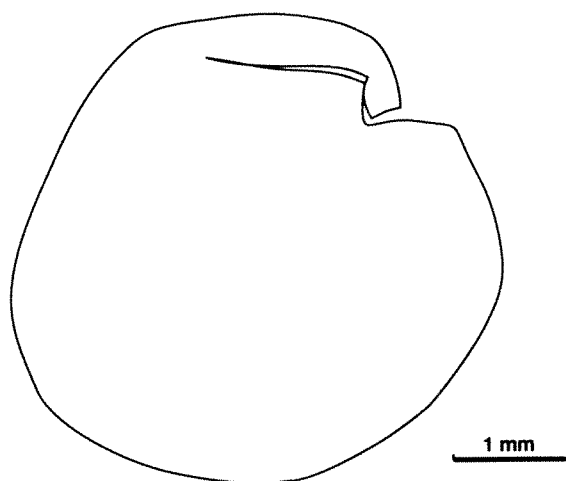
**TABLE 3**  
PREOPERATIVE CORRECTED VISUAL ACUITY

	PATIENTS	
	NO.	%
20/30 to 20/40	6	12
20/40 to 20/70	20	40
20/70 to 20/200	13	26
20/200 or worse	11	22

lotomy had irregular sharp projections and linear tears that extended in a radial direction (Fig. 4). The edge of the capsulotomy specimen showed a lamellar structure aligned parallel to the surface of the lens and adherent lens epithelium (Fig. 5).

**Light microscopy**—By use of light microscopy, the lens-capsule thickness was measured at the anterior pole. Measurements ranged from 10 to 22  $\mu\text{m}$  with a mean of 17  $\mu\text{m}$  (Table 5). Increase in capsule thickness with advancing age was a trend in women and was statistically significant ( $P = .015$ ) in men.

In cross section, the lens epithelium appeared as a monolayer of cuboidal-shaped cells attached basally to the lens capsule (Fig. 6). In sections cut parallel to the surface of the lens capsule, the epithelial cells had a hexagonal distribution (Fig. 7). Epithelial cell diameter was measured as the distance between nuclei of contiguous cells. The mean cell diameter per patient ranged from 10.3  $\mu\text{m}$  to 16.9  $\mu\text{m}$  with a mean cell diameter and standard deviation for the study group of  $13.5 \pm 2.8 \mu\text{m}$ .



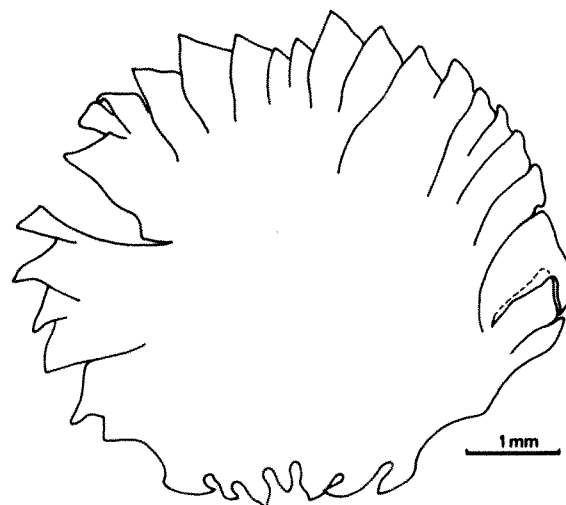
**Fig. 1** (Straatsma and associates). Scale drawing of a continuous-curve capsulotomy (capsulorhexis) specimen.

**TABLE 4**  
PREOPERATIVE STATUS OF THE SURGICAL EYES

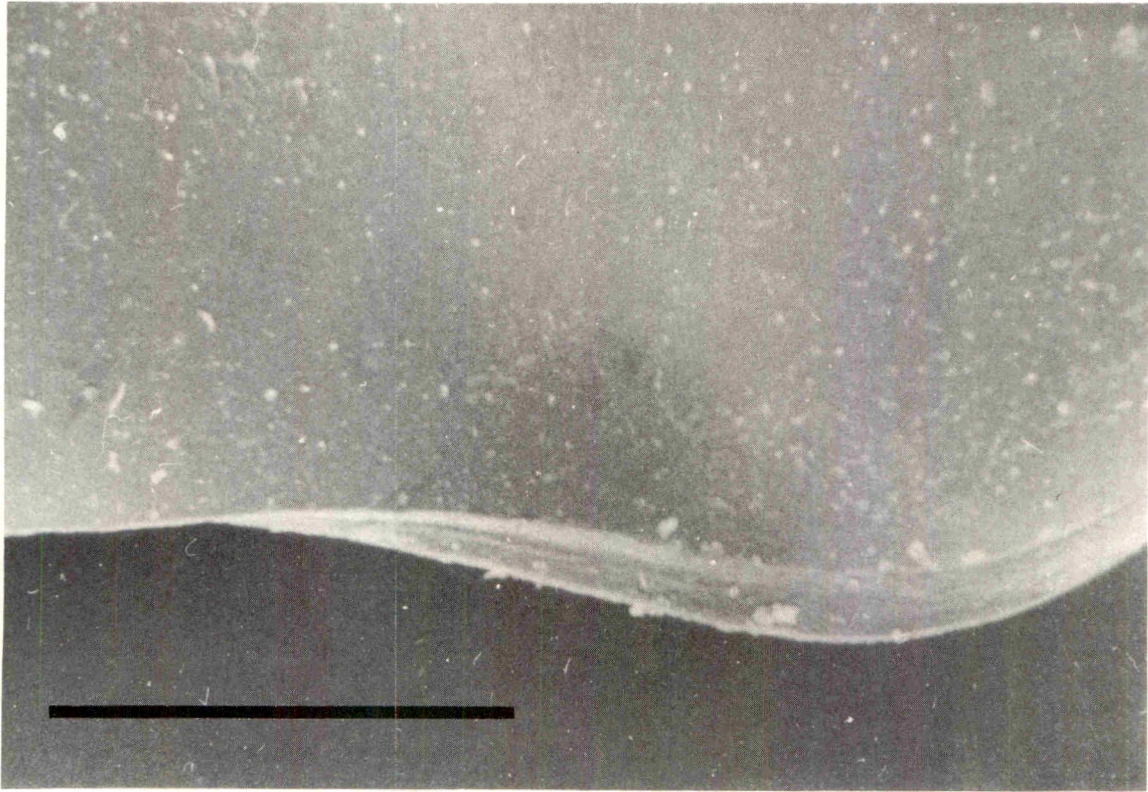
	PATIENTS	
	NO.	%
Retinal surgery	6	12
Macular degeneration	4	8
Eye trauma	3	6
Intraocular inflammation	3	6
Pseudoexfoliation syndrome	2	4
Glaucoma	2	4
Choroidal metastases	1	2

**Transmission electron microscopy**—Ultrastructural examination of the lens capsule disclosed a homogeneous basement membrane-like structure. Epithelial cells were generally cuboidal-shaped in cross section. Lateral borders of the cells were closely joined. Cell apices faced the interior of the lens and were generally separated from the fiber cells of the lens cortex.

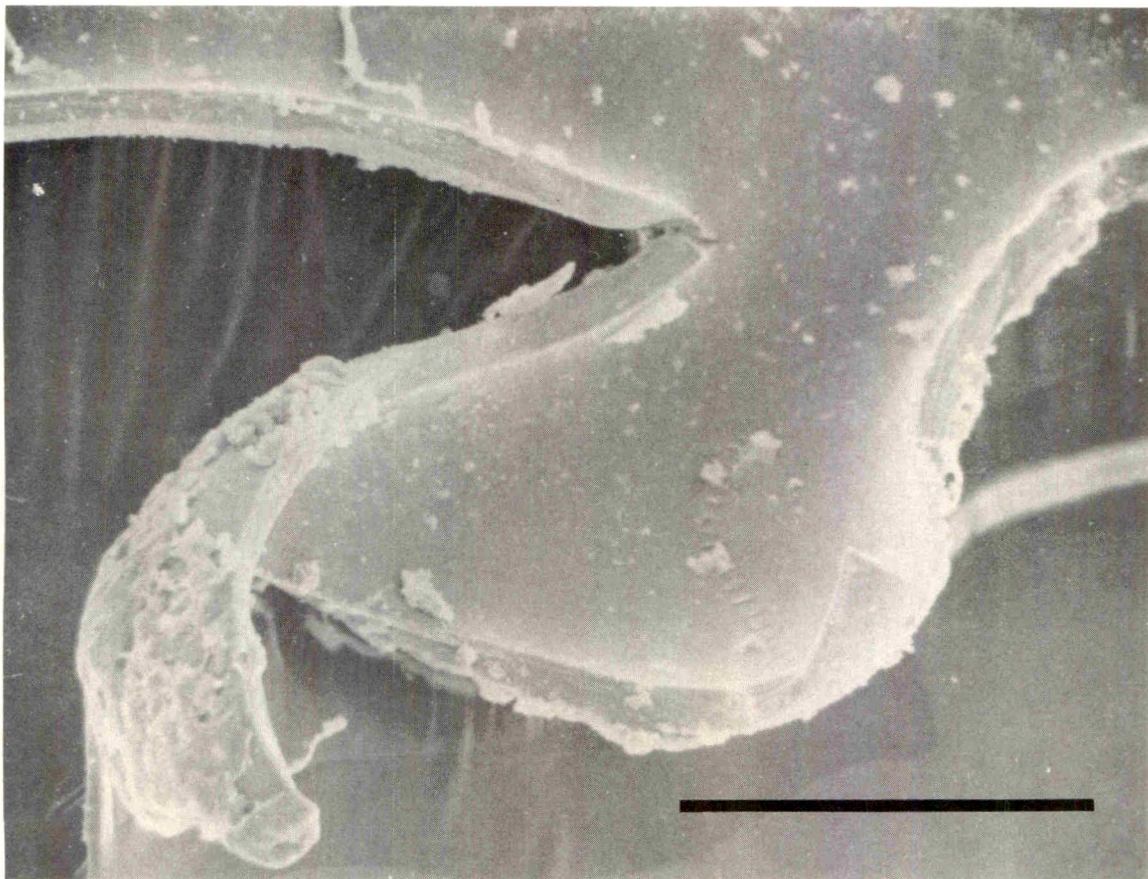
The lens epithelium consisted of normal-appearing (Fig. 8) intermixed with abnormal-appearing epithelial cells. Among the specimens, abnormal cells varied in number and in degree of abnormality. Within single cells, specific organelles also varied in condition. Epithelial cell condition appeared, therefore, to represent a single or local response as contiguous cells often varied in the degree of abnormality. The range of these pathologic changes may be illustrated by use of transmission electron microscopy of normal and abnormal epithelial cell structure (Figs. 8 through 11).



**Fig. 2** (Straatsma and associates). Scale drawing of a multiple-puncture capsulotomy specimen.



**Fig. 3** (Straatsma and associates). Scanning electron micrograph of the smooth edge resulting from continuous-curve capsulotomy. Bar = 0.1 mm.



**Fig. 4** (Straatsma and associates). Scanning electron micrograph of multiple-puncture capsulotomy. The serrated edge with sharp projections and radially oriented tears characterize the multiple-puncture capsulotomy. Bar = 0.1 mm.



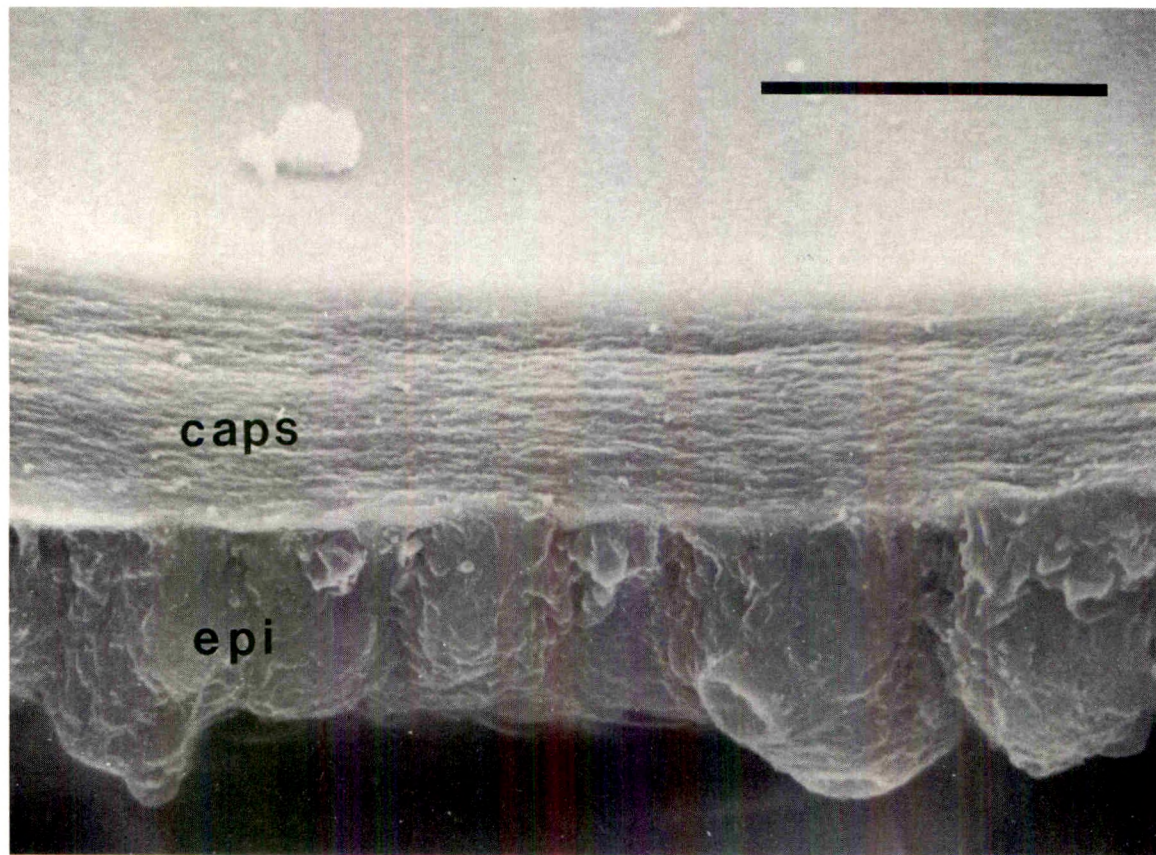


Fig. 5 (Straatsma and associates). Scanning electron micrograph of anterior lens capsule (caps) with adherent cuboidal epithelium (epi). The capsular edge exposed by capsulorhexis continuous tear exhibits a fibrillar structure aligned parallel to the surface. Bar = 20  $\mu$ m.

In the epithelial cell cytoplasm, the rough endoplasmic reticulum ranged from normal-appearing profiles to pathologic structures. The reticulum organelles were usually few in number in normal-appearing cells and showed a few ribosomes along the cytoplasmic surface separated by narrow cisternae. Ribosomes never fully lined the cisternal membrane in the tissue studied. Abnormalities were characterized by dilated and lucent cisternae (Fig. 10). The surrounding cytoplasm often included ribosomes

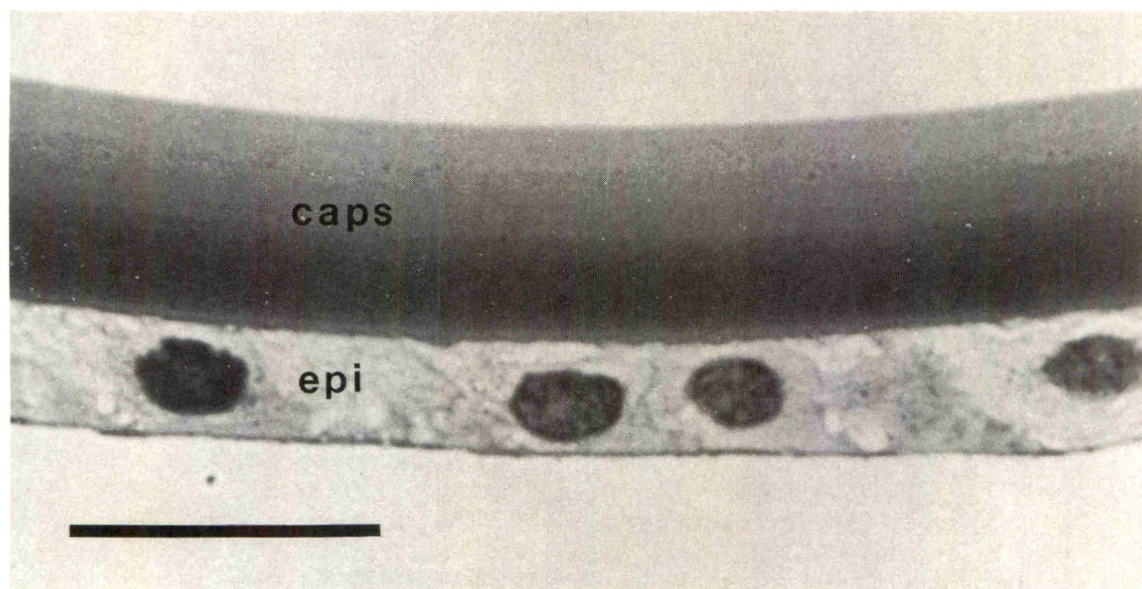
and polyribosomes. Smooth endoplasmic reticulum was observed infrequently.

One to four Golgi figures were found in each cell. The apically located Golgi figures exhibited stacks of lamellar cisternae with adjacent vesicles budding off into the cytoplasm (Fig. 9). In less active-appearing epithelial cells with fewer organelles, the Golgi figures were decreased in number and often showed abnormalities consisting of rounded or swollen cisternae (Fig. 8).

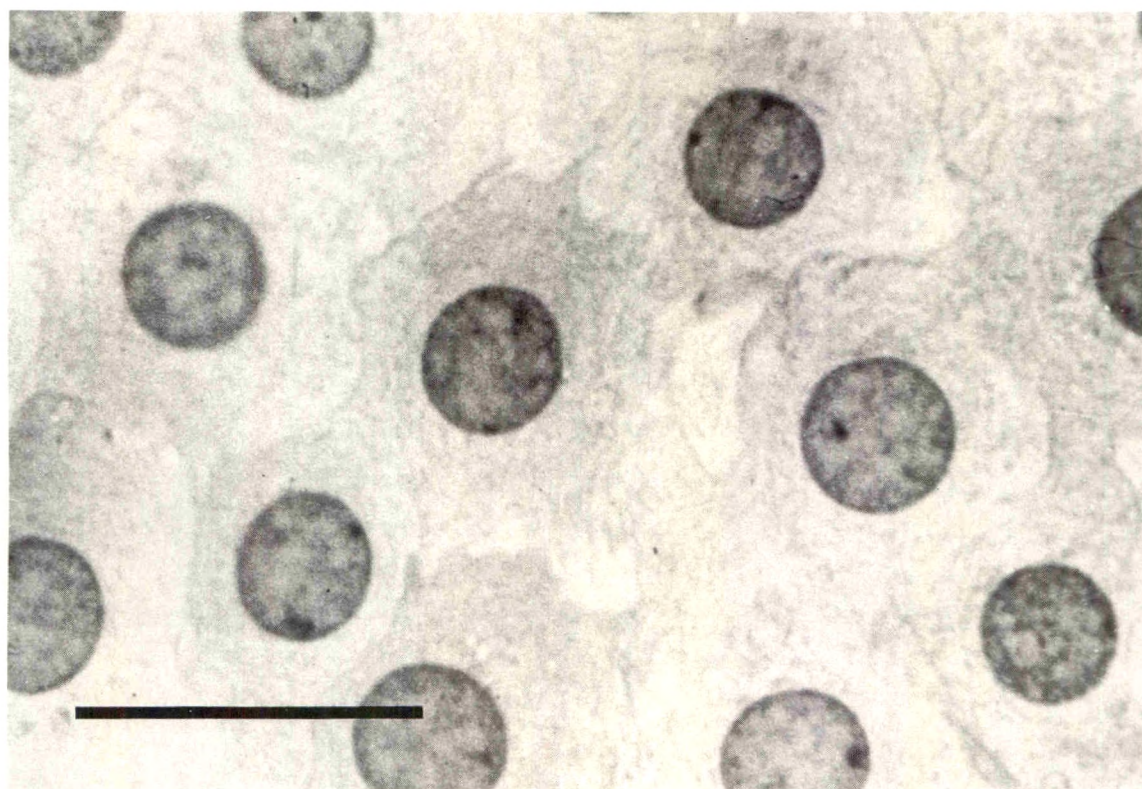
TABLE 5  
CAPSULE THICKNESS BY AGE (YRS) AND GENDER

	< 50		50-59		60-69		70-79		> 80		All
	M	F	M	F	M	F	M	F	M	F	—
No.	1	1	2	0	4	7	10	7	4	8	44
Mean measurement ( $\mu$ m)	10.0	13.8	17.5	—	16.9	15.7	17.0	19.3	21.6	15.9	17.2
Standard deviation	0.0	0.0	1.8	—	3.9	3.1	2.4	3.9	1.9	3.0	3.5



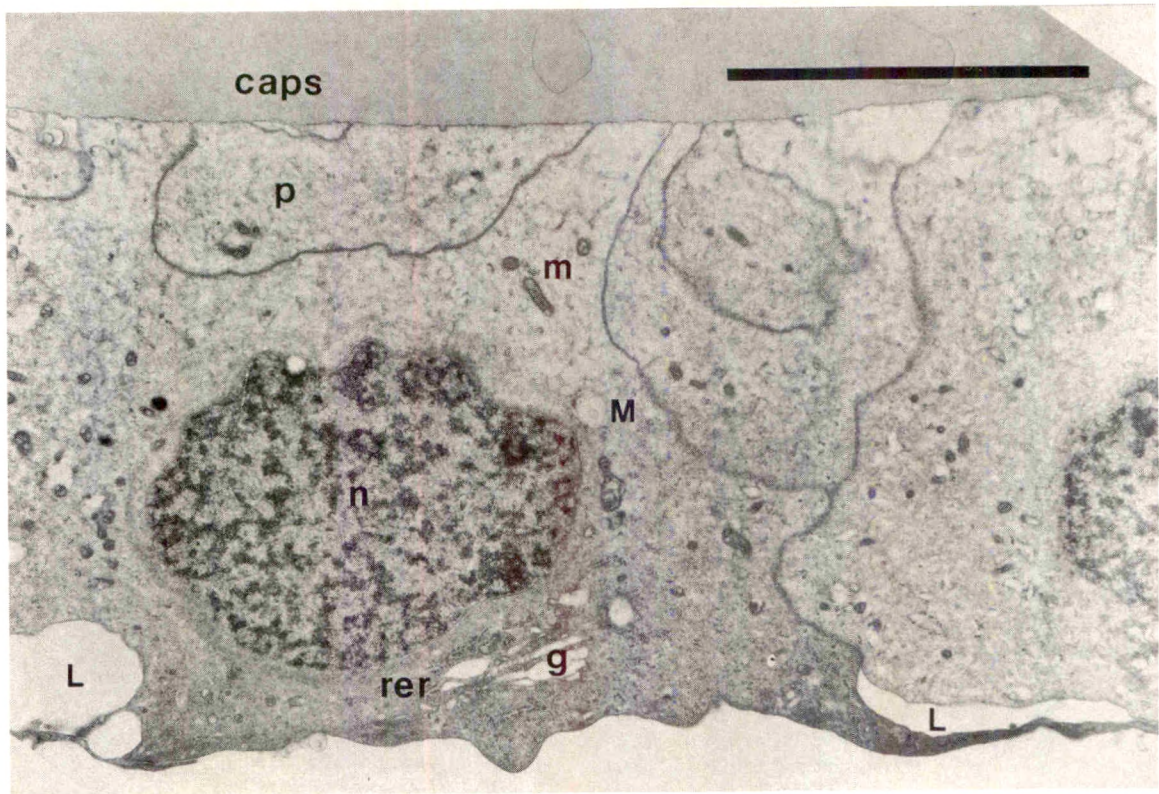


**Fig. 6** (Straatsma and associates). Light micrograph showing a cross section of a capsulotomy sample in this study. The lens capsule (caps) and cuboidal epithelial (epi) cell profiles attached to the posterior (internal) surface are apparent. The reversed curve of the capsule is from retained tension after capsulotomy. Bar = 20  $\mu$ m.

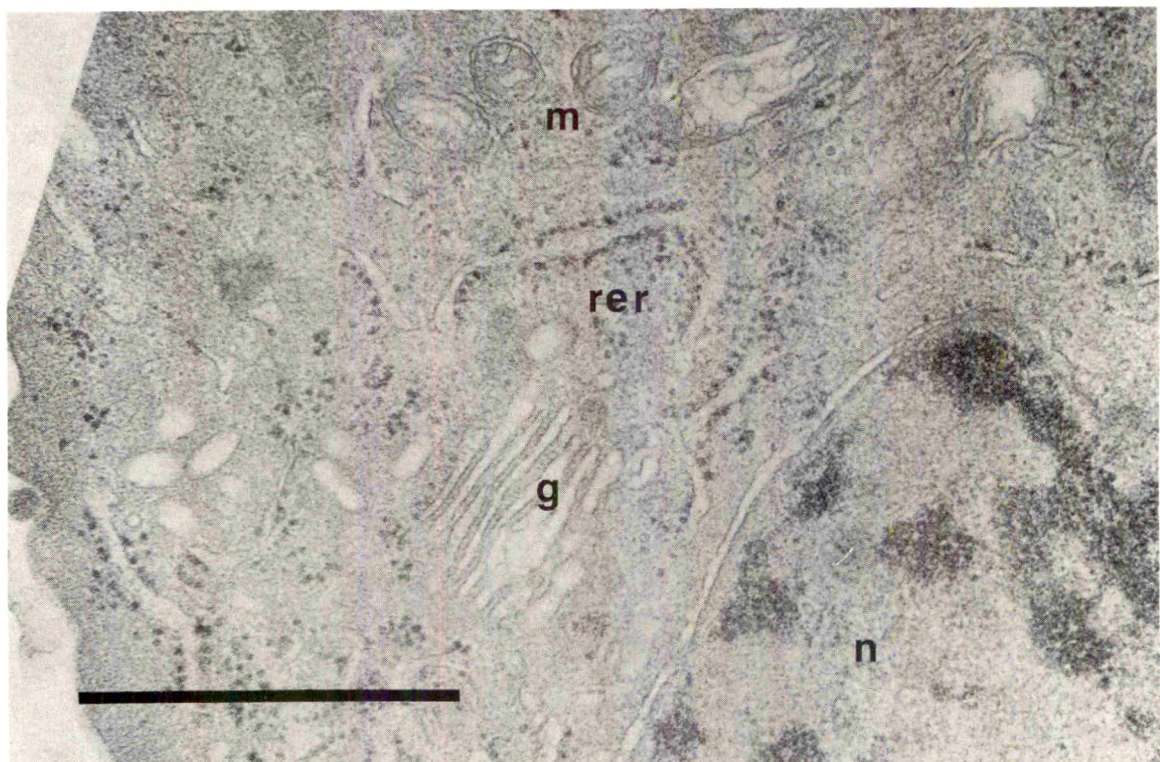


**Fig. 7** (Straatsma and associates). Light micrograph of anterior lens epithelium. The capsulotomy specimen is sectioned tangentially to the anterior lens surface. The regular hexagonal array and interdigitating processes are apparent in this view. Bar = 20  $\mu$ m.



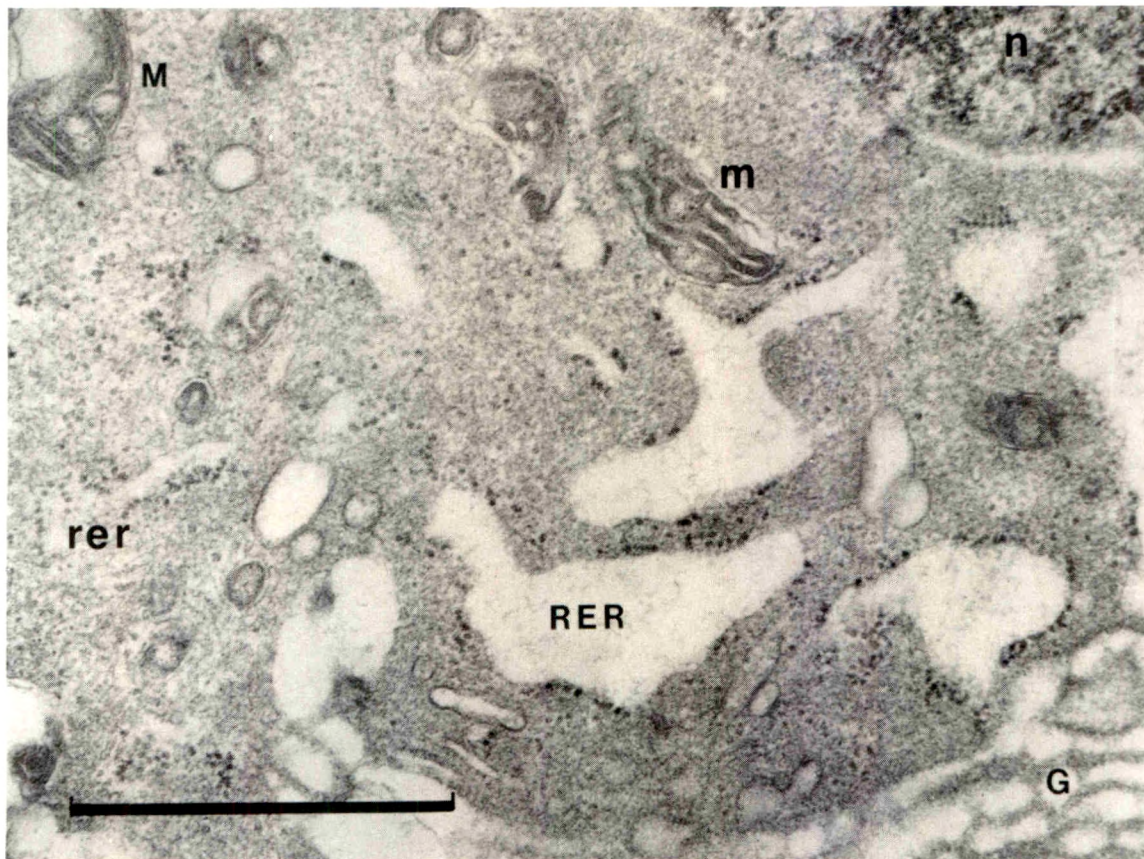


**Fig. 8** (Straatsma and associates). Electron micrograph illustrating aging in lens epithelium. Cuboidal anterior lens epithelial cells show the capsule (caps) basally and the profile of an insinuating process (p) from an adjacent epithelial cell. The lateral apposition is characterized by extracellular lacunae (L). The nucleus (n) is of standard shape and surrounded by a well-formed nuclear envelope. Each cell profile exhibits an apically located and slightly dilated Golgi apparatus (g) surrounded by indistinct profiles of rough endoplasmic reticulum (rer). The appearance of mitochondria ranges from well formed (m) to abnormal appearing with expanded, lucent profiles labeled in capital letters (M). Bar = 5  $\mu$ m.



**Fig. 9** (Straatsma and associates). Electron micrograph high-magnification view of anterior lens epithelium exhibiting normal characteristics. The nucleus (n) chromatin is clumped and the envelope is well formed. The Golgi apparatus (g) is well developed with vesicles budding off apically, and the rough endoplasmic reticulum (rer) is characterized by ribosomes. The mitochondria (m) are abundant and contain well-defined cristae. Bar = 1  $\mu$ m.





**Fig. 10** (Straatsma and associates). Electron micrograph high-magnification view of anterior lens epithelium showing the range of pathologic changes (labeled in capital letters). The nucleus (n) chromatin is dispersed but otherwise normal. The Golgi apparatus (G) is swollen, though plentiful. The rough endoplasmic reticulum ranges from normal-appearing rough endoplasmic reticulum (rer) to abnormal (RER) with dilated profiles and few ribosomes. Mitochondria also exhibit a range of conditions from well-organized cristae in uniform profiles (m) to swollen with electron-lucent cisternae (M). Bar = 1  $\mu$ m.

Mitochondria varied from clinically normal elongated profiles with well-defined cristae to abnormal profiles with disorganized cristae displaced in a dilated chamber of condensed and electron-dense matrix. With further pathologic change, the disrupted cristae were seen to be electron-lucent and expanded profiles (Fig. 10).

In the epithelial cells, profiles of the nucleus were oblong with slight indentations and the clumped chromatin was uniformly distributed. The nuclear envelope was closely opposed to nuclear material and decorated with well-defined nuclear pores.

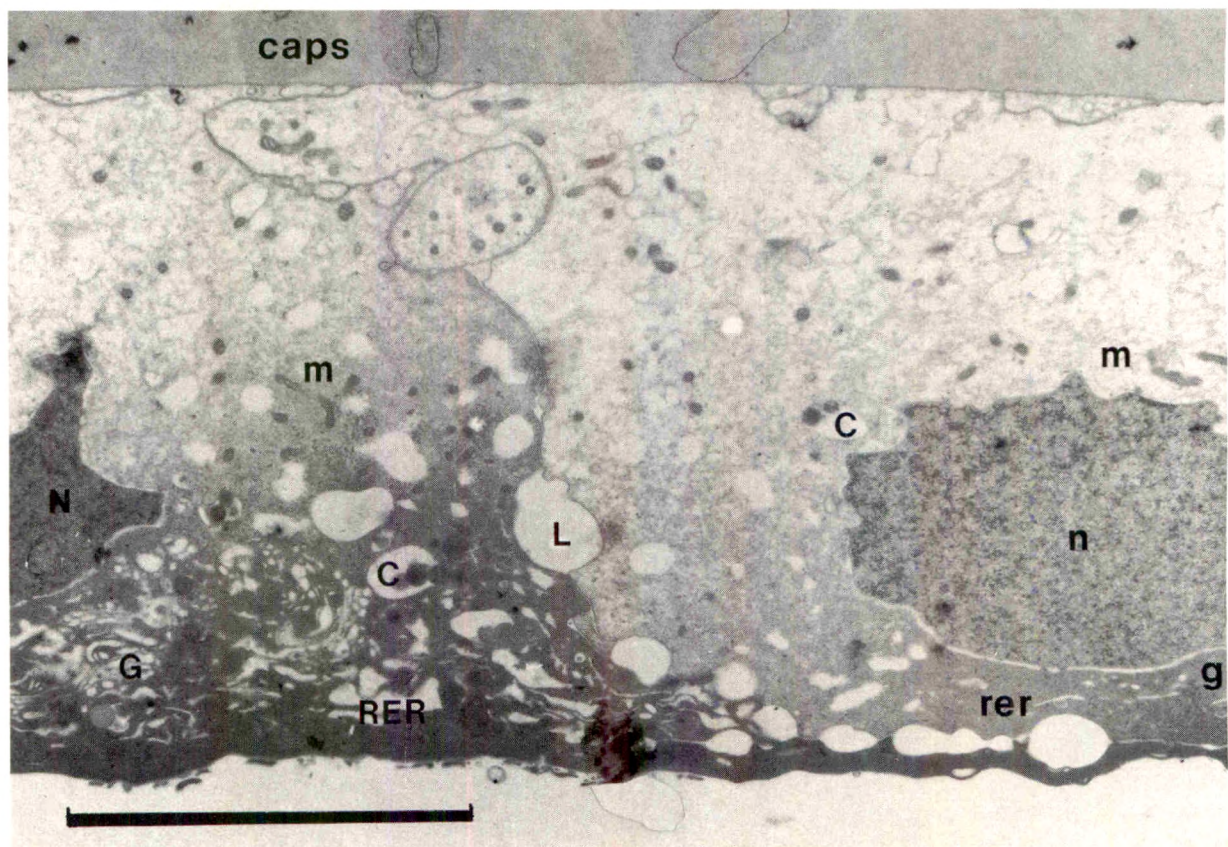
In addition to the study of cytoplasmic organelles and nuclear morphologic structure, extracellular lacunae located between the lateral margins of adjacent cells were examined. Lacunae may be located between normal-appearing epithelial cells (Fig. 8). However, in areas of abnormal epithelial cells, these lacunae were increased in size and number.

As an illustration of major abnormality, one patient with metastatic tumor of the choroid who underwent ocular radiation treatment had a combination of normal-appearing epithelial cells and severely abnormal epithelial cells (Fig. 11). The severely abnormal epithelial cells exhibited a crenated nuclear profile with dispersed chromatin and cytoplasm engorged with multiple abnormal-appearing Golgi figures and vesicles. Lysosomal bodies intruded into lucent intracellular cisternae, and extensive extracellular lacunae were observed.

Three of the 50 specimens had deposits of pseudoexfoliative material. Fibrillar deposits ranged from thin supercapsular layers to extensive bundles with infrequent capsular inclusion (Fig. 12).

*Statistical analysis of lens epithelium ultrastructure*—Lens epithelium ultrastructure was statistically analyzed in 41 of the 50 specimens by study of four to 15 epithelial cells (a mean of





**Fig. 11** (Straatsma and associates). Electron micrograph of anterior lens capsule and epithelium after radiation treatment and chemotherapy for choroidal metastatic tumor with abnormal structural characteristics labeled in capital letters. Abnormal lens epithelial cell exhibiting a crenated nucleus (N) with dispersed chromatin and separated envelope adjacent to a cell with a more normal nuclear profile (n); the Golgi figures (G) and rough endoplasmic reticulum (rer) are extensive and swollen in the left profiles and more normal appearing in the right profiles (rer, g). Intracellular cisternae (C) are characterized by lysosomal bodies in both cells and extracellular lacunae (L) are extensive. Mitochondria (m) appear normal in both cells. The cytoplasm exhibits a gradient of density from the capsule (caps) to the apical margin. Bar = 5  $\mu$ m.

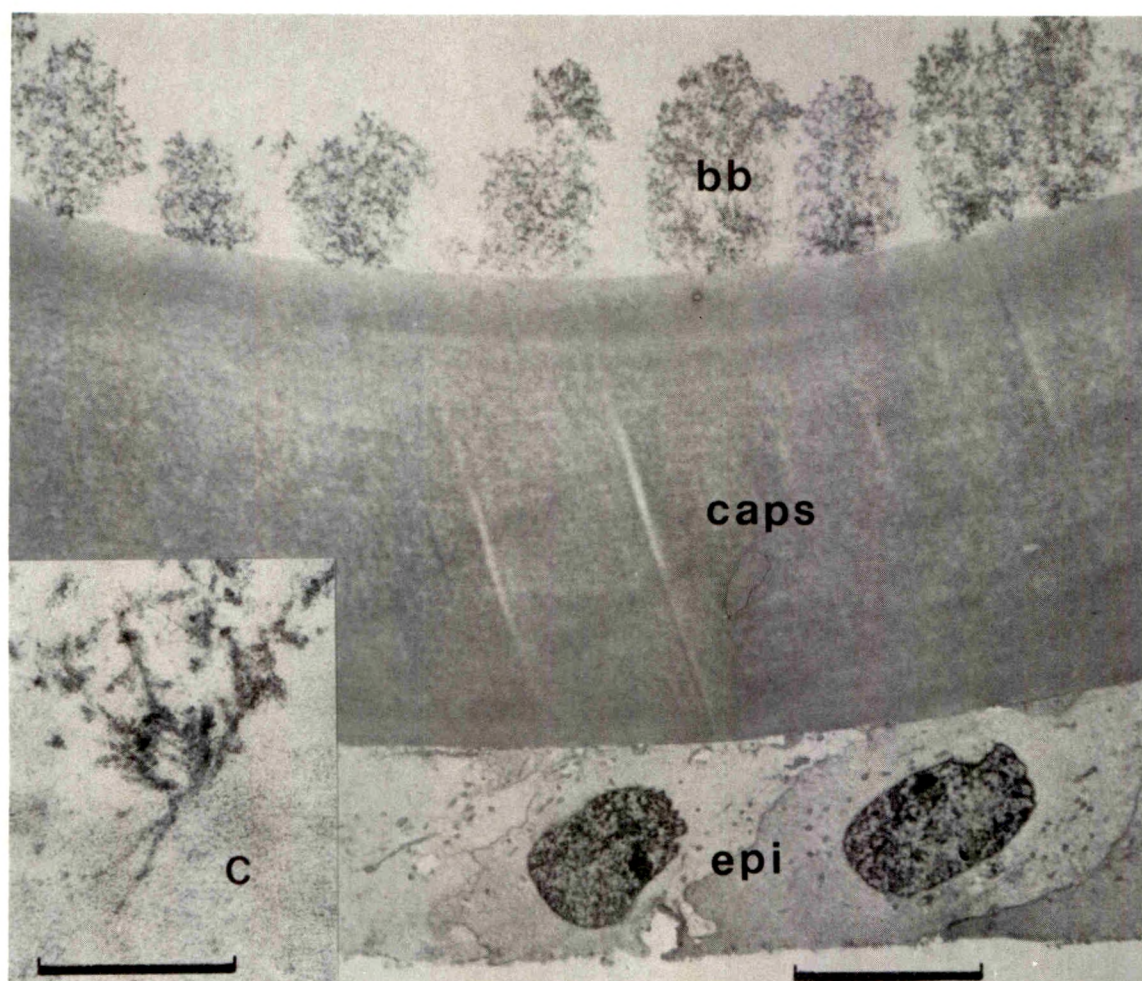
nine cells) in each specimen. These cells, in which there was a central section of the nucleus in the cell profile, were selected at intervals along the full length of the specimen and therefore included the anterior pole of the lens. In each of the study cells, the organelles and ultrastructure were scored for number and condition. Observations confirmed the intermixing of normal (nontumorous) and abnormal (tumorous) epithelial cells and verified the gradation in the quantity and condition of organelles and ultrastructural features.

An index of lens epithelium cytologic activity determined on the basis of quantity of rough endoplasmic reticulum, Golgi apparatus, and mitochondria demonstrated a statistically significant decrease in quantity with advancing age ( $P = .038$ ). The rough endoplasmic reticu-

lum showed an even more statistically significant decrease in quantity with advancing age and an even more statistically significant increase in abnormality with advancing age ( $P = .0001$ ). Other ultrastructural features of lens epithelial cells did not demonstrate statistically significant associations with advancing age.

**Biochemical analysis**—Biochemical analysis consisted of glutathione reductase assay in the lens epithelium with and without supplemental flavin adenine dinucleotide. Glutathione reductase activity was measured and activation coefficients were calculated in lens epithelium. Lens epithelium enzyme activity was measured in 39 of the 50 cataract surgery specimens. In three specimens there was no measurable activity with or without supplement; in two there was activity only with supplement; and in four





**Fig. 12** (Straatsma and associates). Electron micrograph anterior lens epithelium (epi) and capsule (caps) with pseudoexfoliation material on the external (anterior) surface in bundles (bb) of fibrillar material. Bar = 10  $\mu\text{m}$ . Inset, Higher magnification view illustrates inclusion of pseudoexfoliation material into the capsule (c). Bar = 1  $\mu\text{m}$ .

the activity was markedly increased with supplement so that the coefficient was equal to or greater than 1.25. Glutathione reductase activity was present without supplement or not significantly enhanced by supplement in 30 specimens. Thus, glutathione reductase deficiency was marked in nine of 39 (23%) lens epithelium specimens from patients undergoing cataract surgery (Fig. 13).

### Discussion

The patients in this study had a mean age of 75 years; diverse medical features; and multiple cataractogenic factors, including genetic considerations, metabolic diseases, drug treat-

ment, and irradiation treatment. This diversity of medical features and cataractogenic factors is characteristic of other consecutive series of our patients undergoing surgery for age-related cataract.<sup>5</sup>

Anterior capsulotomy was performed by either continuous-curve capsulotomy (capsulorhexis) or multiple-puncture capsulotomy. Ultrastructure study demonstrates that continuous-curve capsulotomy leaves a smooth edge to the specimen and, therefore, to the retained capsular bag. This smooth edge is elastic, so it can be stretched without tearing.

The normal-appearing anterior lens capsule had a generally homogeneous lamellar structure and an average thickness of 17  $\mu\text{m}$ . The increase in capsule thickness with advancing age was statistically significant in men, but



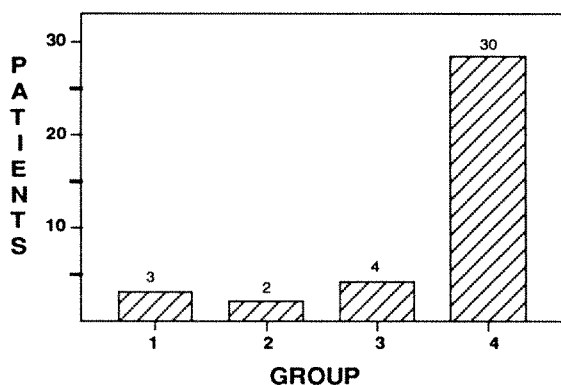


Fig. 13 (Straatsma and associates). Distribution of glutathione reductase activity with or without flavin adenine dinucleotide in 39 cataract surgery patients. Group 1, no measurable glutathione reductase activity with or without supplement; Group 2, activity obtained only after addition of supplement; Group 3, activity markedly increased after addition of supplement; and Group 4, activity without supplement or not markedly increased with supplement.

evident only as a trend in women. The lack of statistically significant increase in capsule thickness with advancing age ( $P = < .05$ ) in women is likely to represent a statistical limitation related to sample size. The findings of capsule production and increased thickness throughout life are well documented.<sup>7,13,14</sup>

Emphasis was placed ultrastructurally on lens epithelium because these cells are the most active metabolic units of the lens. From formation of the lens capsule during the sixth week of gestation throughout the balance of life, lens epithelium is responsible for growth of the lens through mitosis, fiber cell formation, and protein synthesis; active transport of ions and metabolites across the lens capsule; maintenance of lens viability; and control or repair of damage caused by photochemical reactions, oxidation, radiation, trauma, and other injuries.

We found normal-appearing epithelial cells intermixed with abnormal-appearing epithelial cells. Moreover, among the specimens, abnormal cells varied in number and in the extent of abnormality. Previous investigations of epithelium in the adult human lens, including studies of the aging lens and age-related cataract, described relatively inactive-appearing epithelium, but did not note the intermixing of normal and abnormal cells.<sup>6-8,15,16</sup>

One specimen in our study, from a patient with a history of ocular radiation treatment for

metastatic choroidal tumor, showed epithelial cells with an apparent increase in cytologic activity adjacent to normal-appearing epithelial cells. The increased activity was demonstrated by elaborate vacuolation, multiple Golgi vesicles, lysosomal bodies, and increased lacunae. Comparable increase in cytologic activity of lens epithelium in response to radiation exposure,<sup>17,18</sup> and the intermixing of normal and abnormal epithelial cells<sup>19,20</sup> were demonstrated in experimental animal studies of radiation-induced lens changes.

Extracellular lacunae located between lens epithelial cells have been reported, but researchers have questioned whether these are *in vivo*<sup>8,21</sup> or are an artifact of tissue handling.<sup>16</sup> In a preliminary study, we altered the fixative buffer concentration and observed that the lacunae persisted through the full range of osmolarity, beyond concentrations that resulted in swelling of the cell and hypertonic concentrations that resulted in cell shrinkage. Furthermore, in an unpublished study to localize lens proteins in fetal tissue, we observed abundant lacunae containing labeled lens proteins in the anterior polar lens epithelium. These observations suggest that lacunae are present *in vivo* and may represent extracellular storage sites.

As a specific form of histopathologic abnormality, the pseudoexfoliation syndrome was diagnosed clinically in two of the 50 cataract surgery patients and was identified histopathologically in the same two specimens and in one additional specimen in which the process was extremely mild and undoubtedly subclinical. The pseudoexfoliation syndrome was associated histopathologically with dendritic accumulations or bundles of fibrillar material that were on the anterior surface of the lens capsule and sometimes extended as inclusions into the superficial layers of the lens capsule. Abnormalities associated with this elastinlike fibrillar material were consistent with previous descriptions of the pseudoexfoliation syndrome.<sup>22,23</sup> Recent work has helped to clarify the nature of exfoliative material and may lead to understanding its synthesis.<sup>24</sup>

The histopathologic study of lens epithelium in this series of 50 cataract surgery specimens demonstrates a gradient of abnormalities that may be associated with clinically appreciable cataract. These descriptions, however, probably represent only a portion of the range of epithelial cell abnormalities that may be associated with age-related cataract. Moreover, additional studies are required to correlate lens epithelial

abnormalities with the alterations in anterior subcapsular, cortical, and nuclear cataract that were identified clinically in this investigation.

With statistical assessment of ultrastructural features, an index of epithelial cell activity determined by the quantity of rough endoplasmic reticulum, Golgi apparatus, and mitochondria demonstrated a statistically significant decrease in quantity of these organelles with advancing age ( $P = .038$ ). The rough endoplasmic reticulum showed an even more statistically significant degree of abnormality in advancing age group ( $P = .0001$ ). These findings warrant emphasis because they demonstrate age-related retrograde changes in lens epithelium.

Biochemically, the epithelial cells are the most active cells in the lens. The majority of the pumping sites that osmoregulate the lens by discharging sodium are located in the anterior epithelial cell layer. The concentration of enzymes in the lens is highest in the epithelial layer. The lens possesses an elaborate defense mechanism against oxidative injuries. In this system, the highest concentrations of the protective enzymes such as glutathione reductase, glutathione peroxidase, superoxide dismutase, and glutathione-S-transferase are found in the epithelial layer. Our previous work suggested that epithelial glutathione reductase may not be functioning optimally in cataractous lenses.<sup>10</sup> This dimeric enzyme requires flavin adenine dinucleotide for its catalysis, which in turn is biosynthesized from dietary riboflavin.<sup>25</sup> A high activation coefficient ( $\geq 1.25$ ) may reflect dietary deficiency of riboflavin. In agreement with our previous finding,<sup>10</sup> a relatively large percent (23%) of epithelial cell specimens from cataractous lenses in this study showed glutathione reductase deficiency. Although the precise relationship between glutathione reductase activity and cataract is not known, this study demonstrates less than optimal concentrations of this important enzyme in a number of patients undergoing cataract surgery. Whether deficiency of glutathione reductase, possibly secondary to deficiency of riboflavin, is a contributing risk factor in age-related cataract is still open to question, and more studies are needed.

Age-related cataract may be a multifactorial process in which many intrinsic and extrinsic factors act cumulatively, at least in part along common biochemical molecular pathways, to damage the lens and disrupt transparency.<sup>5</sup> Thus, to prevent or retard cataract, risk factors for lens damage should be minimized and bio-

logic defense systems should be maintained at optimal strengths.

Particularly for individuals with intrinsic genetic predisposition to age-related cataract, efforts should be made throughout the full span of life to minimize risk factors such as uncontrolled systemic disease, cataractogenic drugs, ionizing radiation, and unnecessary or excessive ultraviolet and high-energy visible light exposure. To maintain biologic defense mechanisms at best-possible strengths, a balanced nutritional diet with daily dietary allowances of riboflavin and other vitamins should be considered.

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#### OPHTHALMIC MINIATURES

Try as she might, she could never get her eyes to disappear. So what was the point? They were everything. Everything was there, in them. All of those pictures, all of those faces.

Toni Morrison, *The Bluest Eye*  
New York, Simon & Schuster, 1970, p. 39

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# Conjunctival Impression Cytology in Patients With Glaucoma Using Long-term Topical Medication

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William N. Steinmann, M.D., and George L. Spaeth, M.D.

Increasing evidence indicates that long-term use of topically administered medications can induce changes in the conjunctiva and ocular surface. We used the technique of conjunctival impression cytology to evaluate the conjunctival changes that develop with long-term use of topically administered anti-glaucoma medications. Patients with glaucoma who were on a stable regimen of one, two, or three topically administered medications were recruited for study; glaucoma suspects who were not using topically administered medications served as controls. Eyes with clinical or historical evidence of external eye disease or conjunctival surgery were excluded. Impression cytology specimens, collected from the bulbar and palpebral conjunctiva, were coded and subsequently graded by a masked observer. We examined specimens from 72 eyes by using this technique. Aggregate scores for the bulbar conjunctiva were compiled, using a previously described grading system with a range of 0 (normal) to 3 (diffuse, severe metaplasia). The results show statistically significant degrees of conjunctival metaplasia associated with the number of glaucoma medications used. These results suggest that the long-term use of antiglaucoma medications induces changes in the conjunctival surface. These changes may be

related to the medications themselves, the preservatives in the commercial preparations, or the duration of topical treatment. The clinical relevance of these changes remains unknown.

**A**LTHOUGH TOPICALLY ADMINISTERED medications remain the usual treatment in primary open-angle glaucoma, these drugs are not without adverse effects, both ocular and systemic. The systemic adverse effects of several classes of these drugs (for example, systemic  $\beta$ -adrenergic blockade) have been studied extensively. Although some ocular adverse effects (for example, cystoid macular edema in aphakic patients receiving epinephrine) have been identified, remarkably little is known about the effects of long-term use of these drugs on the conjunctiva.

Although clinicians view the conjunctiva as a passive, semipermeable barrier that allows drugs to enter the eye, it is nevertheless a living dynamic tissue that can respond to stress with inflammation, scarring, keratinization, and neovascularization. Virtually all topically administered medications are known to cause conjunctival reactions in some patients. The topically administered drugs used in the treatment of glaucoma are no exception. Particular offenders include echothiophate iodide,<sup>1</sup> dipivefrin hydrochloride,<sup>2</sup> and pilocarpine,<sup>1,3</sup> although the most frequently used class of glaucoma medications, the  $\beta$ -adrenergic antagonists, are also known to cause conjunctival keratinization.<sup>4</sup>

Much anecdotal evidence suggests that the conjunctiva, the ocular surface, or both, of patients using topically administered antiglaucoma medications are altered. Many patients with glaucoma complain of dry eye symptoms when using their medications, yet their tear

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production as measured by Schirmer testing is normal, suggesting that the lipid composition of the tear film has been altered. Conjunctival goblet cells are lost with long-term treatment with pilocarpine,<sup>5</sup> and light and electron microscopy disclose conjunctival changes with long-term  $\beta$ -antagonist treatment.<sup>6</sup> There is *in vitro* evidence that many of the antiglaucoma drugs (and the preservatives used in their formulation) are toxic to conjunctival epithelium in culture.<sup>7</sup>

The conjunctival surface is known to possess regional variations in both cellular distribution and morphologic characteristics. Because of these regional variations, incisional biopsy is limited as a method to examine the conjunctival surface; it is invasive and provides only a cross-sectional view of a single point on the ocular surface.

Conjunctival impression cytology is a method of obtaining cytologic specimens from the conjunctival surface.<sup>8-10</sup> It is safe, painless, and simple, and has provided insights into the conjunctival causes of a number of ocular surface disorders, including xerophthalmia,<sup>11-13</sup> keratoconjunctivitis sicca,<sup>14</sup> squamous metaplasia,<sup>15</sup> conjunctivitis,<sup>16</sup> ocular pemphigoid, Stevens-Johnson syndrome, and others.<sup>17</sup> Electron microscopy of the specimens is possible<sup>18</sup> and sequential study is not difficult.

In this study, we evaluated the conjunctival changes associated with long-term use of antiglaucoma medications, using the technique of conjunctival impression cytology.

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### Subjects and Methods

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The patient protocol and associated informed-consent documents were reviewed and approved by the Institutional Review Board of the Wills Eye Hospital. Consecutive subjects were recruited from the Glaucoma Service of the Wills Eye Hospital. Patients asked to participate included the following: (1) patients with glaucoma who were on a long-term (greater than three months) stable regimen of topically administered glaucoma medications that included one or more of the three basic classes of glaucoma medications: epinephrine or dipivefrin,  $\beta$ -adrenergic antagonists, and miotics; and (2) patients being monitored as glaucoma suspects who were receiving no topical treatment. Patients were excluded from the study for the following reasons: (1) age under 18 years; (2) any history of surgery or other interventions

such as cryotherapy that might cause conjunctival scarring; (3) use of any topically administered medications not among the classes previously described, including artificial tear preparations; or (4) any history or slit-lamp examination evidence of ocular surface disorder (that is, ocular pemphigoid, keratoconjunctivitis sicca, or herpes) predating the diagnosis and treatment of glaucoma.

Informed consent was obtained from the patients who participated. On entering the study, a detailed ocular history was obtained, emphasizing medication history, as well as symptoms and clinical signs of ocular surface disorders. Each patient received a careful slit-lamp examination by one of us to identify any ocular surface abnormalities or evidence of external eye disease. Data were recorded in a standardized format and coded for later retrieval.

We performed impression cytologic examination of the topically anesthetized conjunctiva according to the technique described by Nelson.<sup>10</sup> Small (6.2 mm) disks of cellulose acetate filter paper were placed on the bulbar conjunctiva after topically administered anesthesia was achieved. Four bulbar conjunctival specimens were obtained just adjacent to the corneoscleral limbus nasally, temporally, inferiorly, and superiorly. Specimens of the inferior palpebral conjunctiva at the center of the lower eyelid were obtained.

The five specimens from each eye were then attached to microscope slides with double-sided tape so that their positions on the slide corresponded to the location from which the specimen was obtained. Specimens were then fixed with cytologic spray fixative and stored for later staining.

The specimens were stained, examined, and graded by one of us (J.R.W.) according to the technique and grading scheme outlined by Nelson.<sup>10</sup> The examiner was masked to the clinical or medical history of the patient from whom the specimen was taken.

The impression cytology grades from the four bulbar specimens were averaged for an individual bulbar score; the single palpebral conjunctival specimen grade was analyzed alone. Statistical comparison between cases and controls was performed by use of Student's unpaired *t*-test.

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### Results

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We recruited 50 patients to participate in the study. Specimens in which two or more of the

five cytologic specimens obtained per eye that were judged unreadable were discarded. After excluding 28 individual eyes that met the exclusion criteria listed, we analyzed the impression cytology data from a total of 72 eyes.

Comparison of the four groups disclosed similar ages (Table). The control group, consisting of patients suspected of having glaucoma and who were receiving no topically administered medication, had the lowest cumulative impression cytology score, a finding that was consistent with a healthy conjunctiva.

The impression cytology grade of three of the four treatment groups ( $\beta$ -blockers,  $\beta$ -blockers and pilocarpine, and maximal treatment) all demonstrated a statistically significant increase in cytologic grade compared to the control group (Table). The group of patients receiving a combination of a  $\beta$ -blocker and epinephrine/dipivefrin had a cytologic grade only slightly higher than the control group, and this difference was not statistically significant ( $P = .175$ ).

Palpebral and bulbar conjunctival cytologic grades were determined in all five groups (Figure). The largest difference between treatment group and control is seen in those patients receiving maximal treatment, suggesting a relationship between the number of medications and the cytologic grade.

### Discussion

Our results confirm the clinical impression that the ocular surfaces of patients receiving long-term topical treatment for glaucoma are abnormal. Our data suggest a relationship between the number of medications and the severity of conjunctival changes observed.

In obtaining medication histories, we found

that most patients could not recall the specific duration of individual treatments. This information was not available from the patients' charts, as most had received much of their care elsewhere before being referred to us. Because most patients receiving maximal treatment had been under medical treatment longer than those on single-drug treatment, our findings may be more closely related to the overall duration of topical treatment rather than to the individual components of that treatment.

One strength of this study was that the grading of specimens was done in a masked fashion. However, interpreting the statistical (and clinical) relevance of the findings is hampered because the grading system we used is a subjective one that simply divides cytologic appearance into four categories. We do not fully understand the natural history of conjunctival metaplasia. If grades 2 and 3 represent metaplastic changes that are at the far end of the cytologic spectrum (for example, 95 and 99 on a scale of 100), then our findings are perhaps more significant than  $P$  values alone would indicate. Conversely, if grade 2 represents metaplasia at the lower portion of the cytologic spectrum, our results may be less significant.

The cause for the apparent effect of long-term topical treatment for glaucoma on the conjunctiva is not known. The glaucoma drugs themselves or the preservative common to their commercial preparations, benzalkonium chloride, may be responsible. We suspect that benzalkonium chloride has a large role in the development of the conjunctival changes we have demonstrated. Of importance is that the only treatment group that did not demonstrate a statistically significant increase in cytologic grade was that in which a  $\beta$ -adrenergic antagonist was combined with an adrenergic agonist (epinephrine/dipivefrin). Perhaps some of the

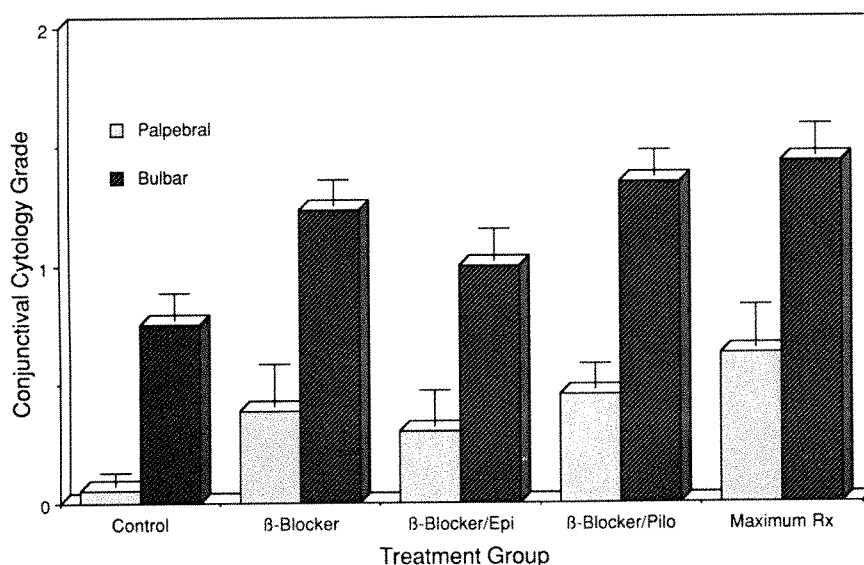
TABLE  
AGGREGATE IMPRESSION CYTOLOGY SCORES BY TREATMENT GROUP

TREATMENT GROUP	NO. OF EYES	AGE (YRS)	BULBAR CONJUNCTIVA	PALPEBRAL CONJUNCTIVA
Controls	19	69.5 $\pm$ 12.8	0.75 $\pm$ 0.11	0.05 $\pm$ 0.05
$\beta$ -blockers alone	13	67.2 $\pm$ 7.6	1.23 $\pm$ 0.11*	0.39 $\pm$ 0.18*
$\beta$ -blockers and epinephrine/dipivefrin	10	73.6 $\pm$ 9.8	1.00 $\pm$ 0.13	0.30 $\pm$ 0.15
$\beta$ -blockers and pilocarpine	22	67.8 $\pm$ 8.3	1.35 $\pm$ 0.12†	0.46 $\pm$ 0.11*
Maximal treatment	8	73.9 $\pm$ 6.4	1.44 $\pm$ 0.13†	0.63 $\pm$ 0.18†

\* $P = .05$  compared to control.

† $P = .001$  compared to control.





**Figure** (Brandt and associates). Graph comparing the conjunctival impression cytologic grade of both bulbar and palpebral conjunctivae in the patient groups studied.

conjunctival changes we have demonstrated are mediated at the adrenergic receptor.

The impact of these conjunctival changes on the outcome of filtering surgery is clinically important, because most patients undergo surgery only after months or years of topical drug treatment. Successful glaucoma-filtering surgery depends on many technical and host factors, not the least of which is the existence of a healthy conjunctiva. Long-term conjunctival inflammation and scarring, whether results of underlying ocular disease, previous surgery, or drug-induced toxicity such as pseudophthalmoid, are known to predispose patients to poor outcome after filtration surgery.<sup>19</sup> Recent animal studies<sup>20</sup> demonstrated an increase of myofibroblastic cell proliferation in fistulized rabbit conjunctiva treated with glaucoma medications or a preserved artificial tear compared with untreated controls. Sherwood and associates<sup>21</sup> reported on the morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in patients undergoing trabeculectomy. Results of biopsies in patients who had been on long-term topical treatment showed an increase in macrophages, fibroblasts, lymphocytes, and mast cells and decreased conjunctival goblet cells compared with patients who had received little if any preoperative drug treatment. In a related report, Lavin and associates<sup>22</sup> found that filtering surgery was more successful in patients who had received an average of only two weeks of preoperative medical treatment compared with patients who had received at least one year of medical treatment.

It is often difficult to identify those patients who are at increased risk of surgical failure after trabeculectomy. Our study results suggest that impression cytology may be useful in identifying conjunctival changes related to long-term drug use, and further studies will be needed to determine whether these changes are predictive of surgical outcome.

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# A Clinical Trial of Metipranolol, a Noncardioselective Beta-Adrenergic Antagonist, in Ocular Hypertension

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In randomized, double-masked fashion, 24 volunteers with ocular hypertension received 0.3% or 0.6% metipranolol, a noncardioselective beta blocker; or placebo twice daily to both eyes for six weeks. Intraocular pressure (mean  $\pm$  SEM) was reduced ( $P = .01$ ) in the metipranolol-treated patients (baseline measurement,  $25.9 \pm 0.5$  mm Hg to  $18.1 \pm 1.2$  mm Hg at six weeks, 0.6% concentration; baseline measurement,  $27.1 \pm 0.4$  mm Hg to  $21.6 \pm 1.5$  mm Hg at six weeks, 0.3% concentration). Intraocular pressure was not markedly changed in placebo-treated patients. Outflow facility was unaltered two hours after instillation of metipranolol at study week 2 compared to baseline measurement. Aqueous humor flow rates were reduced ( $P = .02$ ) 20% after 0.6% or 0.3% metipranolol instillation and were unchanged after placebo administration compared to baseline measurement. Mean systolic blood pressure, diastolic blood pressure, and pulse rate were not markedly altered. Metipranolol reduces intraocular pressure by suppressing aqueous humor flow rates.

**M**ETIPRANOLOL IS A noncardioselective beta-1 and beta-2 adrenergic antagonist,<sup>1</sup> similar in receptor selectivity to timolol and levobunolol. Metipranolol has recently been released under the tradename of OptiPranolol (Bausch and Lomb, Tampa, Florida) in the United States as a 0.3% solution for intraocular pressure reduction. This drug has been marketed in Europe for

over ten years as a topical agent for glaucoma and as an oral agent for cardiovascular disease. Previous clinical investigations of topically applied metipranolol have been performed outside of the United States. The majority of these trials have been uncontrolled,<sup>2-5</sup> and had inadequate prestudy glaucoma-treatment washout periods.<sup>5-8</sup> The mechanism by which metipranolol reduces intraocular pressure is presumed to be reduction of aqueous humor flow rates; this has not been confirmed clinically.

This double-masked, randomized study evaluated the effects on intraocular pressure of administration of two concentrations of metipranolol (0.3% and 0.6%) compared to administration of placebo, in patients with ocular hypertension. The mechanism by which this drug reduces intraocular pressure was investigated in these patients.

The study was reviewed and approved by the Mount Sinai Medical Center Institutional Review Board for clinical trials.

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## Patients and Methods

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Patients with ocular hypertension were selected. Ocular hypertension was defined as intraocular pressures of 24 mm Hg or greater, full Goldmann visual fields, and optic-nerve cupping that was not suggestive of glaucomatous damage. The diagnosis of ocular hypertension had to precede the study by at least three months. Open angles, as determined by gonioscopy, were required. Exclusion criteria included corneal disease precluding reliable applanation tonometry, secondary forms of glaucoma, and previous laser treatment or intraocular surgery. Patients with asthma, obstructive pulmonary disease, or a history of sensitivity to beta-adrenergic antagonists were excluded.

Each patient had an initial examination and at least two screening examinations before ad-

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mission into the study. The initial examination included a medical and ocular history, a brief ophthalmic examination, and discontinuation of use of any ocular hypotensive medications. Screening examinations were initiated at least one week after the use of glaucoma medications was discontinued. Each patient had to meet the intraocular pressure requirements on two screening examinations and the baseline examination. The intraocular pressure requirements for enrollment were 24 mm Hg or greater in both eyes, with a difference of 5 mm Hg or less between the two eyes and a 20% increase in intraocular pressure in both eyes after discontinuation of the prestudy use of glaucoma medications. The qualifying intraocular pressure was the average of two measurements taken one hour apart between 8:00 A.M. and 11:00 A.M. Drug was dispensed at the baseline examination if the patient fulfilled all study criteria. The patients were randomly assigned to receive 0.3% or 0.6% metipranolol or placebo. Patients were instructed to instill the medication at 8:00 A.M. and 8:00 P.M. daily, except on study examination days. At treatment examination weeks 2, 4, and 6, the examiner measured intraocular pressure two hours after instillation of the morning dose of medication. At week 5, the intraocular pressure was measured before the morning instillation of medication. The final examination at week 6 consisted of an intraocular pressure measurement taken 24 hours after the last dose of medication. At the baseline examination and each subsequent study examination, blood pressure and pulse rate were measured, and volunteered and elicited symptoms were recorded.

Ophthalmic examinations included visual acuity, accommodation, pupil size, corneal anesthesia measured with an aesthesiometer (Cochet-Bonnet, Luneau, France), and external and slit-lamp examinations. Additionally, at the baseline examination medical history, cardiac and pulmonary auscultation, gonioscopy, and Goldmann visual fields were performed. At the baseline and final examinations, additional testing included Schirmer tear testing and dilated ocular examination. Outflow facility was measured with an electronic tonograph at the baseline examination, and two weeks after beginning treatment, two hours after the morning application of drug. Aqueous humor flow rates were measured with the Coherent Fluorotron Master (Palo Alto, California) and calculated, using the software program of Yablonski and associates.<sup>9</sup> The anterior chamber volume and

corneal volume were calculated for each patient from corneal thickness and anterior chamber-depth measurements taken by use of pachymeters (Haag-Streit, Bern, Switzerland).<sup>10</sup> These values were used in the aqueous flow rate calculations. Aqueous flow rate measurements were performed one week before initiating treatment and three weeks after initiating treatment. Patients instilled one drop of 10% fluorescein every five minutes for a total of five drops the evening preceding flow rate measurements. Flow rate measurements were begun at 8:30 A.M., and repeated every half hour for 2½ hours. Twenty-four patients with ocular hypertension were enrolled and completed this six-week comparison trial of twice-daily administration of 0.3% metipranolol, 0.6% metipranolol, and placebo.

For each patient, data analysis was performed on the average of the two eyes. The level of significance was determined, using the Student two-tailed paired *t*-test.

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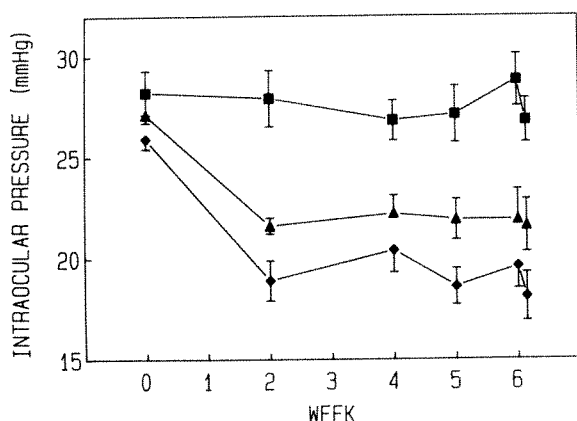
## Results

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*Patient demographics*—The mean ( $\pm$  S.E.) age of the participants was  $64.8 \pm 1.8$  years, with a range of 49 to 79 years. Fifteen of the patients were men and nine were women. Four patients were white, 11 were black, and nine were Hispanic. Twenty of the patients had dark irides. The mean prestudy baseline intraocular pressures were  $28.2 \pm 1.1$  mm Hg in the placebo-treated patients,  $27.1 \pm 0.4$  mm Hg in the 0.3% metipranolol-treated patients, and  $25.9 \pm 0.5$  mm Hg in the 0.6% metipranolol-treated patients. Five patients in the placebo-treated group and three patients in each of the two metipranolol-treated groups were treated with glaucoma medications before admission into the study. Differences in patient demographics in any of the three treatment groups were not statistically significant.

*Aqueous humor dynamics*—Twice-daily administration of 0.3% or 0.6% metipranolol significantly ( $P = .05$ ) reduced intraocular pressure at all study examinations compared to baseline measurements (Fig. 1). Intraocular pressure was not reduced in the placebo-treated patients at any study examination. The maximum reductions in intraocular pressure were from  $27.1 \pm 0.4$  mm Hg at baseline measurement to  $21.6 \pm 0.4$  mm Hg at week 2 and  $21.6 \pm 1.3$  mm Hg at week 6 in the 0.3% metipranolol-





**Fig. 1** (Serle, Lustgarten, and Podos). The effect of 0.3% metipranolol (triangles) (N = 8), 0.6% metipranolol (diamonds) (N = 8), and placebo (squares) (N = 8) on intraocular pressure in patients with ocular hypertension. Points represent average pressure of right eye and left eye and the limits  $\pm$  standard error of the mean. Asterisk indicates statistically significant reduction in intraocular pressure compared to baseline measurements; two-tailed paired *t*-test, *P* = .05.

treated patients, and from  $25.9 \pm 0.5$  mm Hg at baseline measurement to  $18.1 \pm 1.2$  mm Hg at six weeks in the 0.6% metipranolol-treated patients.

Mean outflow facility was not significantly (*P* = .21) altered in any of the three treatment groups after two weeks of treatment compared to baseline measurements (Table 1). After three weeks of treatment, fluorophotometrically determined aqueous humor flow rates were significantly (*P* = .02) reduced from  $2.0 \pm 0.1$   $\mu$ l/min to  $1.6 \pm 0.1$   $\mu$ l/min in the 0.6% metipranolol-treated patients and from  $2.4 \pm 0.2$   $\mu$ l/min to  $1.9 \pm 0.2$   $\mu$ l/min in the 0.3% metipranolol-treated patients compared to baseline prestudy measurements (Fig. 2). Aqueous humor flow rates were not reduced significantly (*P* = .11) in the placebo-treated patients.

**Other variables**—Corneal sensitivity measured with a Cochet-Bonnet aesthesiometer was diminished in two eyes of the 0.6% metipranolol-treated patients and in none of the 0.3% metipranolol-treated or placebo-treated patients six weeks after commencing treatment as compared to baseline measurements.

Ocular symptoms were volunteered and elicited from all three treatment groups (Table 2). Burning eyes, photophobia, ocular foreign-body sensation, blurred vision, ocular pain, ocular dryness, and dry mouth were reported

**TABLE 1**  
THE EFFECT OF METIPRANOLOL ON OUTFLOW FACILITY IN PATIENTS WITH OCULAR HYPERTENSION\*

TREATMENT	OUTFLOW FACILITY (MEAN $\mu$ L/MIN/MM HG $\pm$ SEM)	
	BASELINE VALUE	AT THREE WEEKS
Placebo (N = 8)	$0.16 \pm 0.03$	$0.12 \pm 0.01$
0.3% Metipranolol (N = 8)	$0.16 \pm 0.01$	$0.18 \pm 0.03$
0.6% Metipranolol (N = 8)	$0.13 \pm 0.02$	$0.15 \pm 0.02$

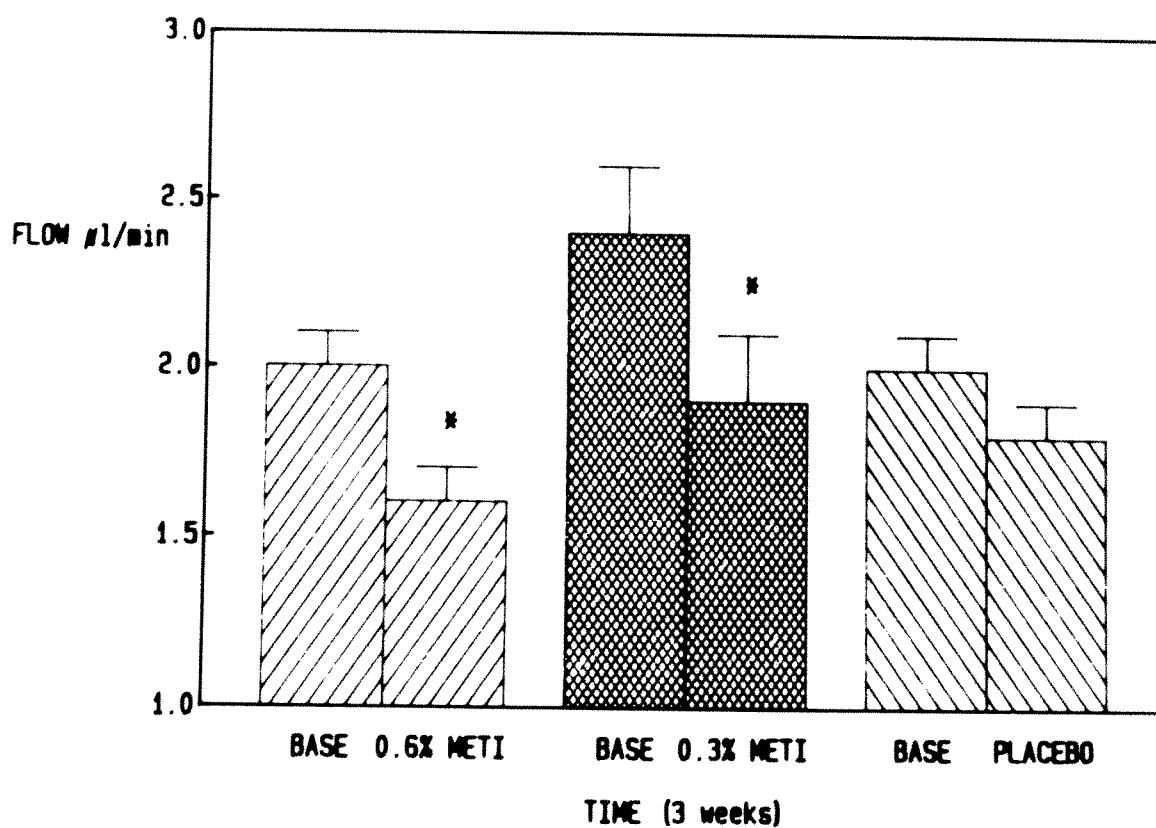
\*No significant changes from baseline measurements in any of the three treatment groups.

more frequently by the 0.6% metipranolol-treated patients than by the other two treatment groups.

Reductions in systolic and diastolic blood pressure and pulse rate were seen in all three study groups compared to baseline measurements. The greatest reduction in systolic blood pressure was from  $133.3 \pm 5.7$  mm Hg at baseline measurement to  $116.8 \pm 3.4$  mm Hg at six weeks in the placebo-treated group. The greatest reduction in diastolic blood pressure was from  $76.6 \pm 2.9$  mm Hg at baseline measurement to  $69.5 \pm 2.3$  mm Hg at six weeks in the 0.3% metipranolol-treated group. The greatest reduction in pulse rate was from  $69.0 \pm 2.9$  beats per minute to  $63.6 \pm 3.1$  beats per minute in the 0.6% metipranolol-treated group. There were no marked differences in the mean changes from baseline measurement of these variables among the three treatment groups.

## Discussion

In this study, 0.3% metipranolol reduced intraocular pressure up to 21%, and 0.6% metipranolol reduced intraocular pressure up to 31% in patients with ocular hypertension treated bilaterally, twice daily for six weeks. Intraocular pressure was reduced 12 hours and 24 hours after dosing. The open-label administration studies of 0.3% or 0.6% metipranolol demonstrated similar lowering of intraocular pressure in patients with ocular hypertension or glaucoma treated twice daily for up to 48 weeks.<sup>2,3,8</sup> Intraocular pressure reductions of this magnitude have been demonstrated in patients with glaucoma or ocular hypertension



**Fig. 2** (Serle, Lustgarten, and Podos). The effect of 0.3% metipranolol ( $N = 8$ ), 0.6% metipranolol ( $N = 8$ ), and placebo ( $N = 8$ ) on aqueous humor flow rates in patients with ocular hypertension. Bars represent average flow of right eye and left eye and the limits  $\pm$  standard error of the mean. Asterisk indicates statistically significant reduction in aqueous humor flow rates compared to baseline measurements; two-tailed paired  $t$ -test,  $P = .02$ .

treated with timolol, levobunolol, and betaxolol. A one-year comparison trial of 0.25% timolol with 0.25% levobunolol in 78 patients demonstrated mean intraocular pressure reductions of 18% to 20%.<sup>11</sup> In a randomized, double-masked study, 0.25% betaxolol administered for six weeks to 22 patients reduced intraocular pressure up to 21%.<sup>12</sup> A double-masked 26-week comparison study in 46 patients demonstrated reductions of intraocular pressure of 29% with 0.5% betaxolol and 33% with 0.5% timolol.<sup>13</sup> Levobunolol 0.5% or 1% and timolol 0.5% reduced intraocular pressure by 27% when administered twice daily for four years.<sup>14</sup>

The interpretation of several direct comparison trials of metipranolol with timolol or levobunolol is hampered by absent or abbreviated glaucoma drug washout periods and small patient populations.<sup>15</sup> In these trials,<sup>3,5-7,16,17</sup> intraocular pressure was reduced from 15% to 24%, using concentrations of 0.1% to 0.6% metipranolol, and from 12% to 26%, using concen-

trations of 0.25% timolol. Intraocular pressure was reduced by 29% in 46 patients treated with 0.6% metipranolol or 0.5% levobunolol in a 12-week comparison study.<sup>18</sup>

The aforementioned studies suggest that the efficacy of metipranolol is comparable to the other beta blockers currently used in the treatment of glaucoma. Metipranolol, like levobunolol, has an active metabolite<sup>19</sup> and may have an extended duration of effect on intraocular pressure. Except for a lower cost,<sup>20</sup> it is not clear if metipranolol offers any particular advantages over these other agents. Well-controlled trials comparing the safety of metipranolol to other beta-adrenergic antagonists must be performed.

Timolol,<sup>21-24</sup> levobunolol,<sup>25,26</sup> and betaxolol<sup>26,27</sup> reduce intraocular pressure by decreasing aqueous humor flow rates. It has been presumed that metipranolol has a similar mechanism of action. This study demonstrated that metipranolol 0.6% suppresses aqueous humor flow rates by up to 21% after three weeks of



**TABLE 2**  
OVERALL INCIDENCE OF VOLUNTEERED AND  
ELICITED COMPLAINTS DURING THE STUDY

	TREATMENT GROUP		
	PLACEBO (N = 8)	0.3% METIPRANOLOL (N = 8)	0.6% METIPRANOLOL (N = 8)
<b>Ocular complaints</b>			
Itching eye	6	2	5
Burning eye	1	2	6
Photophobia	3	2	5
Foreign-body sensation	1	3	4
Blurred vision	1	1	5
Eye pain	2	0	4
Tearing	3	0	1
Dryness	1	0	3
<b>Nonocular complaints</b>			
Headache	4	2	4
Dry mouth	2	2	5

twice-daily administration and does not alter outflow facility.

The blood pressure and pulse rates of the patients treated with metipranolol were not substantially altered compared to placebo-treated patients. The 0.6% metipranolol-treated patients had a higher incidence of volunteered and elicited ocular side effects than the 0.3% metipranolol or placebo-treated patients. Substantial adverse ocular or systemic effects were not encountered during the study.

Metipranolol is an effective ocular hypotensive agent. Long-term safety studies and additivity studies need to be completed to determine if this drug is as useful as, or possibly preferable to, the other available beta-adrenergic antagonists in certain clinical situations.

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#### OPHTHALMIC MINIATURE

When the Creator of the Universe  
came to Earth,  
when It resolved to be born  
as a male human infant  
in a stable  
attached to a busy inn,  
It had never had need for eyes before.  
It had known all things and been all things.  
The Creator had only to exist.  
That was enough.  
But now, as a human infant,  
It was also going to see—  
and to do so imperfectly,  
through two human eyes,  
each a rubbery little camera.

Kurt Vonnegut, *Sun Moon Star*  
New York, Harper & Row Publishers, 1980



# Isolating the Effects of Primary Open-angle Glaucoma on the Contrast Sensitivity Function

Pamela A. Sample, Ph.D., Pascal S. C. Juang, B.S., and Robert N. Weinreb, M.D.

We evaluated spatial contrast sensitivity functions in age-matched and lens density-matched healthy eyes, eyes with primary open-angle glaucoma, and eyes with ocular hypertension. We also controlled for refraction, visual acuity, pupil size, and previous ocular history. We found an overall reduction in contrast sensitivity for the glaucomatous eyes with a significant difference at 12 cycles per degree ( $P < .012$ ). Eyes with ocular hypertension were not significantly different from normal eyes. Significant differences were noted at several spatial frequencies with less careful controls for age and lens effects. We concluded that spatial contrast sensitivity may be a useful adjunctive diagnostic test for glaucoma, but interpreting the results without other clinical data may lead to errors in diagnosis.

ONLY A SMALL NUMBER of ocular hypertensive eyes will be diagnosed subsequently with primary open-angle glaucoma.<sup>1-3</sup> Moreover, some eyes with high intraocular pressure demonstrate histopathologic evidence of glaucomatous optic nerve damage despite normal visual fields.<sup>4,5</sup> These findings have heightened our awareness of the need to develop diagnostic tests that both identify the ocular hypertensive eyes that are at particular risk for developing glaucoma and detect progression of early glaucomatous damage. Measurement of spatial contrast sensitivity has been recommended as a potentially useful test for this purpose.<sup>6-11</sup>

Contrast sensitivity should be a useful test for identifying damage resulting from glauco-

ma.<sup>12,13</sup> Histopathologic evidence has suggested that the large retinal ganglion cell axons (optic nerve fibers) are susceptible to damage in glaucoma.<sup>4,5</sup> Additionally, cells in the magnocellular layer of the lateral geniculate nucleus, which receive input from retinal ganglion cells through these large optic nerve fibers, are most sensitive to luminance contrast. Therefore, increasing dysfunction of large optic nerve fibers should lead to a reduction in luminance contrast sensitivity.<sup>14,15</sup> In clinical practice, however, tests of contrast sensitivity are difficult to interpret because of confounding variables and the large number of other ocular abnormalities that affect the function, such as diabetic retinopathy, cataract, and age-related macular degeneration.

Arden<sup>6</sup> and Arden and Jacobsen<sup>7</sup> were among the first to report the influence of retinal disease on the grating contrast threshold. They found low spatial-frequency deficits in patients with glaucoma, and they also noted a positive correlation between this abnormal contrast sensitivity and cup/disk ratio, visual field loss, and age. Subsequent reports, however, did not find the test suitable for screening glaucomas.<sup>16,17</sup> Sokol, Domar, and Moskowitz<sup>18</sup> found no differences between patients with glaucoma and age-matched normal controls. Stamper, Hsu-Winges, and Sopher<sup>19</sup> found significant differences between normals, glaucoma suspects, and glaucoma patients, but the overlap among the groups was so great that they concluded the test had little diagnostic value.

One possible explanation for these discrepant results is the use of the Arden grating test, which does not include spatial frequencies beyond 6.4 cycles per degree. More recent studies have shown that higher spatial frequencies are more susceptible to glaucomatous damage, showing significant differences among glaucoma eyes, eyes with ocular hypertension, and normal control eyes.<sup>20-22</sup> Others, however, continue to find no significant differences, differences that were too small to be of diagnostic

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value, or differences that were difficult to interpret.<sup>23-26</sup>

These diverse results may, in part, be caused by patient selection and other factors that may have confounded interpretation. In the current study, we controlled for surgery, medication, refraction, lens density, pupil size, visual acuity, and age in an attempt to isolate changes in contrast sensitivity function caused primarily by the presence of primary open-angle glaucoma.

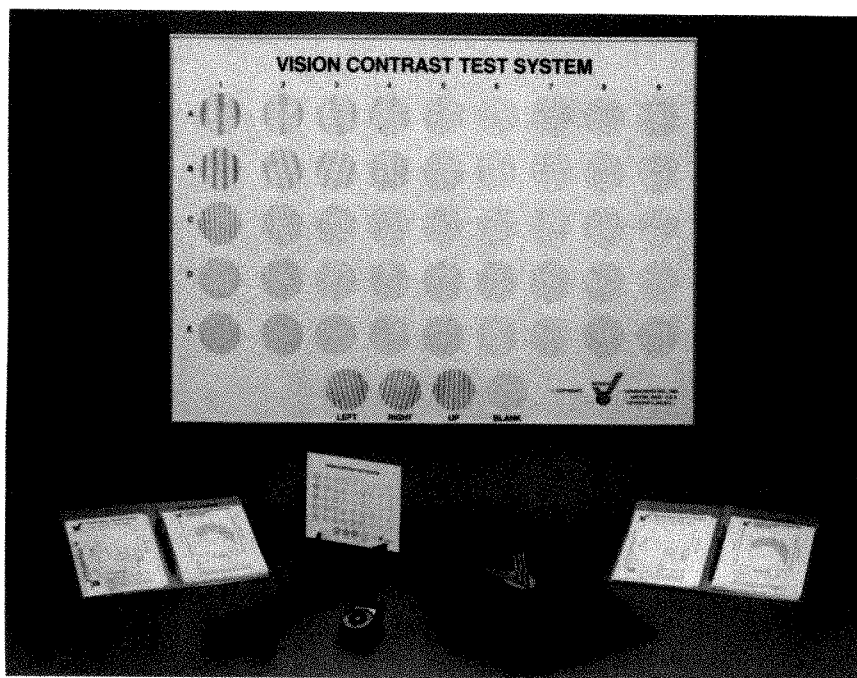
### Material and Methods

The contrast sensitivity function was measured by using the Vision Contrast Test System 6000 (Vistech Consultants, Dayton, Ohio). This test was chosen because it is rapid,<sup>27</sup> encompasses spatial frequencies to 18 cycles per degree, and compares favorably to more elaborately controlled tests.<sup>28</sup> Additionally, the test distance is similar to that used during testing for visual field, color vision, and lens density. The test plate is a small 17.5 × 14.0-cm printed card consisting of five rows of circular targets. Each row has a single spatial frequency, ranging between 1.5 and 18.0 cycles per degree (Fig. 1). The most left target in each row is a high-contrast exemplar, and the eight other targets

in each row have successively lower contrasts; the most right target is a blank. The four-alternative, grating-orientation, forced-choice technique used with this test is designed to reduce the probability of a correct guess, thereby minimizing observer bias. The plate was viewed at a constant luminance specified by the manufacturer (30 to 70 foot-lamberts), measured with a light meter.

This project was approved by the Human Subjects Committee at our institution. The nature of the procedures was fully explained, and informed consent was obtained from each subject.

One eye was selected randomly for study in each subject. After patching the control eye, optimal refractive correction at the working distance of 18 inches was obtained for the selected eye. The pupil size of the test eye was measured with either the telescope and measuring target provided on a perimeter or with a closed-circuit infrared camera system.<sup>29</sup> Eyes with pupil diameters less than 3 mm were excluded. Mean pupil diameters (mean ± standard deviation) were 4.19 ± 0.75 mm for healthy subjects, 4.43 ± 1.09 mm for suspects, and 4.31 ± 1.02 mm for glaucoma subjects. Pupil size did not significantly change with age in these subjects. Eyes being treated with miotic medications underwent a 48-hour wash out period before testing. All other ocular medica-



**Fig. 1** (Sample, Juang, and Weinreb). The Vistech 6000 Contrast Sensitivity Function Test showing the test card and holder. (Reprinted with permission from Vistech Consultants, Dayton, Ohio).



tions were continued. To obtain an index of lens density for each eye, we used a previously described and validated procedure.<sup>29-31</sup> Values of lens density are reported in units relative to 0.00 lens density on the lens density index, the value for a clear lens. Higher numbers correspond to increasing opacity of the lens. A 1-unit change on the index is equivalent to a 0.1-log unit change in lens density.

Two methods for matching groups were used. Group 1 consisted of 43 normal eyes, 31 eyes with primary open-angle glaucoma, and 20 glaucoma-suspect eyes. These 94 subjects were matched for age (normals,  $59.67 \pm 9.79$  years; suspects,  $61.85 \pm 8.28$  years; and glaucoma subjects,  $63.81 \pm 11.33$  years) and lens density

(normals,  $0.67 \pm 0.38$  unit; suspects,  $0.64 \pm 0.41$  unit; and glaucoma subjects,  $0.80 \pm 0.41$  unit). These matches for age are much more stringent than many reported in the literature. However, to reduce further the effects of these variables, a direct matching method was used. In Group 2, a subset of 25 eyes with primary open-angle glaucoma and 20 suspect eyes from Group 1 were each matched to a healthy eye, which was nearly identical in age and lens density. Mean ages and standard deviations were  $60.28 \pm 10.91$  and  $59.72 \pm 11.86$  for paired healthy and glaucoma eyes, respectively, and  $61.20 \pm 8.48$  and  $61.85 \pm 8.28$  for healthy and suspect eyes, respectively. Mean units on the lens density index and standard deviations

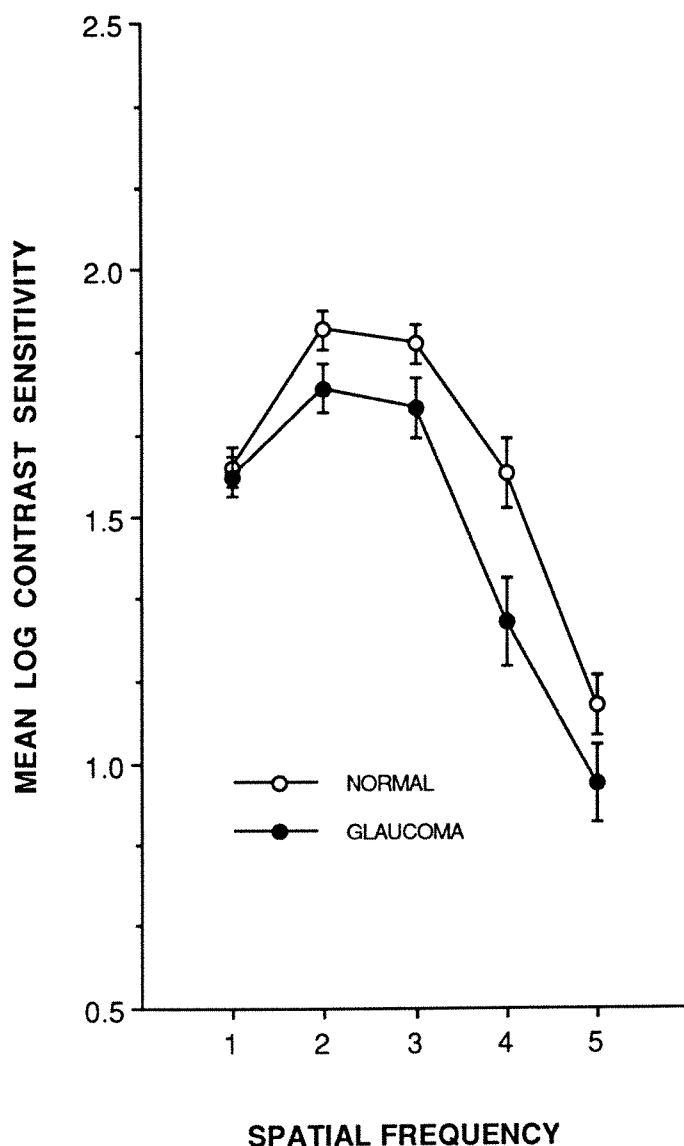
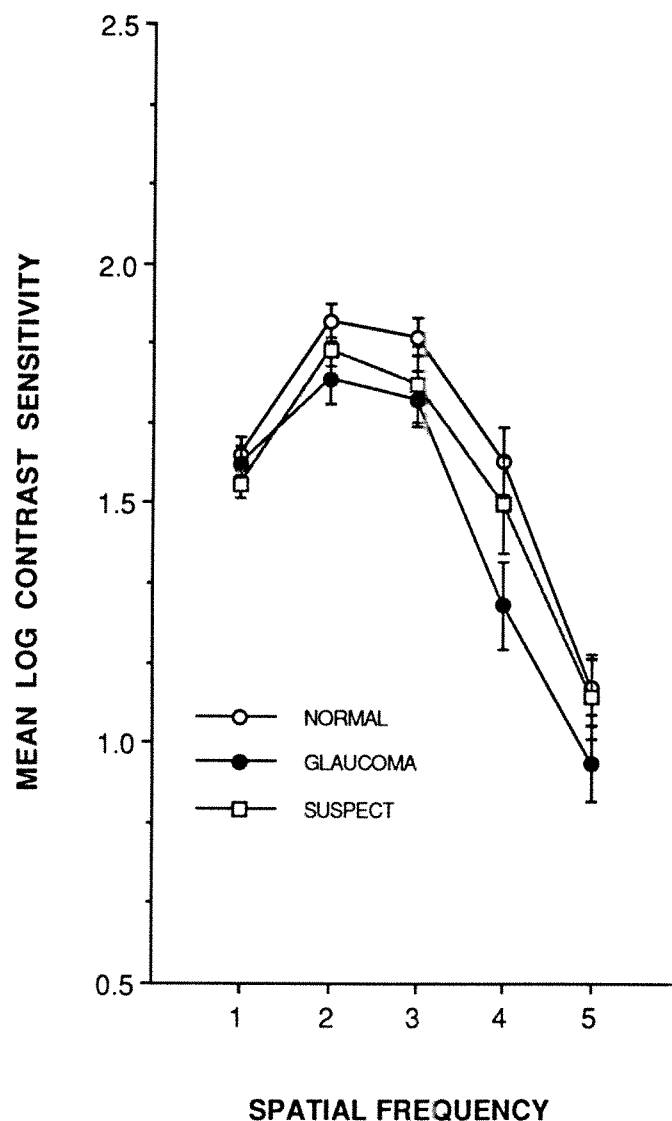


Fig. 2 (Sample, Juang, and Weinreb). The mean log contrast sensitivity function for normal and glaucoma eyes in Group 1. Error bars denote standard error of the mean.



**Fig. 3** (Sample, Juang, and Weinreb). The mean log contrast sensitivity function for normal, suspect, and glaucoma eyes in Group 2. Error bars denote standard error of the mean.

were  $0.68 \pm 0.34$  and  $0.69 \pm 0.38$  for the paired healthy and glaucoma eyes, respectively, and  $0.63 \pm 0.39$  and  $0.64 \pm 0.41$  for the healthy and suspect eyes, respectively.

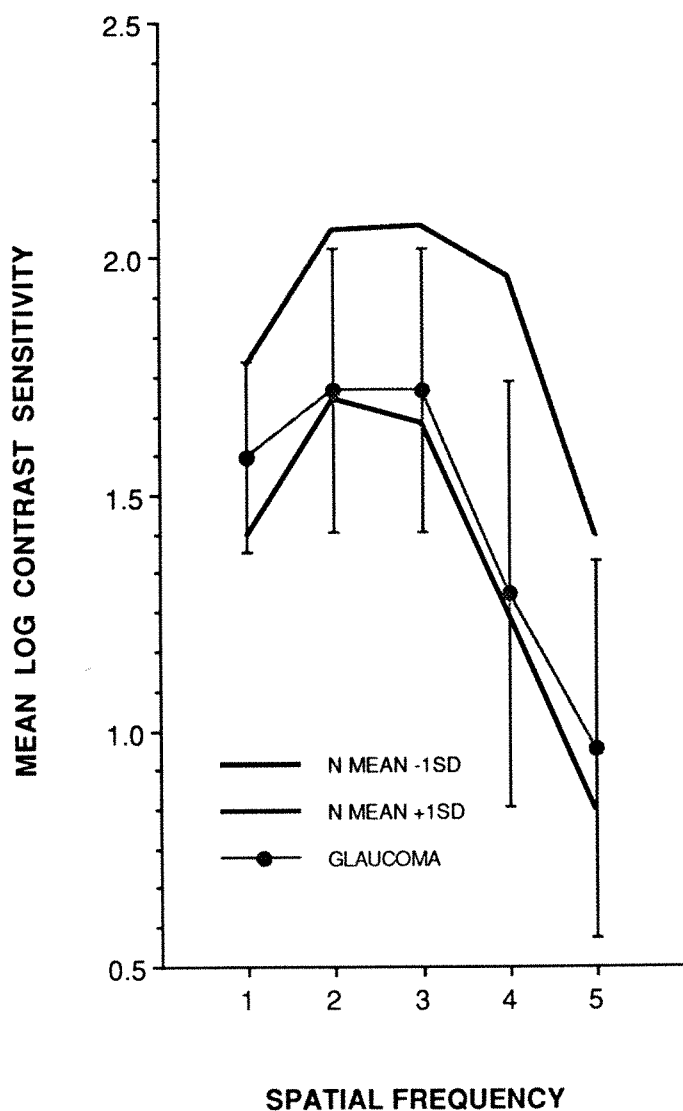
All eyes had a complete examination including best-corrected visual acuity, slit-lamp biomicroscopy, applanation tonometry, and ophthalmoscopy. All subjects had a corrected visual acuity of 20/20. Subjects with ocular abnormalities other than primary open-angle glaucoma or with a history of ocular surgery were excluded from the study. Only those with intraocular pressures less than 21 mm Hg, normal optic nerve heads, normal visual fields, and no family history of glaucoma were considered normal. Glaucoma-suspect patients had normal visual fields and normal optic nerve heads with

intraocular pressures exceeding 24 mm Hg on at least two separate occasions. Patients with primary open-angle glaucoma had glaucomatous optic nerve head abnormalities, characteristic visual field loss, and intraocular pressure exceeding 24 mm Hg on at least two occasions. Differences between groups were evaluated by analysis of variance (unweighted means for Group 1). A P value of less than .05 was considered significant.

## Results

*Group 1:* Thresholds for contrast sensitivity were significantly different overall for healthy





**Fig. 4** (Sample, Juang, and Weinreb). Mean log contrast sensitivity for glaucoma eyes with the normal range for Group 2 ( $\pm 1$  standard deviation).

eyes and eyes with glaucoma ( $P < .001$ ) with analysis at individual spatial frequencies showing significantly increased thresholds at 3 ( $P < .004$ ), 12 ( $P < .013$ ), and 18 ( $P < .036$ ) cycles per degree (Fig. 2). Healthy and suspect eyes were not significantly different at any spatial frequency. No significant differences were observed between the 36 men and 33 women.

**Group 2:** A comparison between Figure 2 (Group 1) and Figure 3 (Group 2) shows that the separation between the curves is somewhat greater for Group 2, although it falls below significance at 1.5, 3, 6, and 18 cycles per degree, probably because of the smaller sample size that results from such stringent one-to-one matching. Of interest, however, is that the significant difference remains between healthy

and glaucoma eyes at 12 cycles per degree ( $P < .012$ ). The difference between healthy and glaucoma eyes for the overall contrast sensitivity function was also significant ( $P < .001$ ). Suspect and healthy eyes did not significantly differ. Mean values for glaucoma eyes did not fall more than 1 standard deviation below that for healthy eyes (Fig. 4), although specific patients did.

Another interesting result was that a certain percentage of patients showed a kink in their function even though sensitivities were within normal limits (Fig. 5). A kink was defined as a deviation from the normal shape of the contrast sensitivity function at one spatial frequency (3, 6, or 12 cycles per degree) with recovery at both lower and higher spatial frequencies. Figure 6

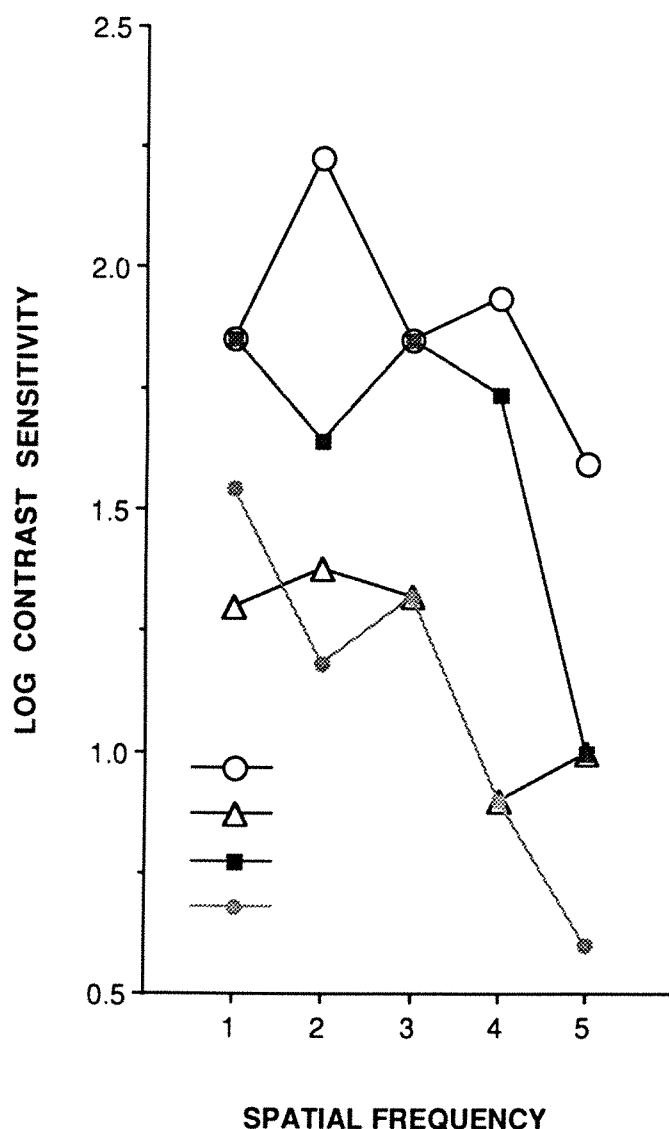


Fig. 5 (Sample, Juang, and Weinreb). Examples of contrast sensitivity functions that show a kink in the curve. Open circles and triangles indicate two subjects who fall within 1 standard deviation of normal at all spatial frequencies. The squares and shaded circles indicate those subjects who fall outside the normal range.

gives the percentage of eyes in Group 2 with sensitivities greater than 1 standard deviation below normal or with a kink. Of the 25 glaucoma eyes, 19 were either more than 1 standard deviation below normal or had a kink in their curve.

### Discussion

A reduction in the contrast sensitivity function in patients with primary open-angle glaucoma was first reported by Campbell and Green.<sup>32</sup> Since that time it has been extensively studied to determine its effectiveness as a test for glaucoma. Some reports show significant

differences between glaucoma and normal eyes. Others show no significant differences. The discrepancies in the reported results can usually be attributed to differences in methodologies or in poor control for other variables that affect the contrast sensitivity function.<sup>22,23,33,34</sup> A good review of problems found in many studies can be found in the report by Owsley, Sekuler, and Seisman.<sup>35</sup>

Glaucoma is not the only ocular disorder that influences contrast sensitivity.<sup>36</sup> Patients with diabetic retinopathy showed reduced contrast sensitivity functions when compared to age-matched controls.<sup>37</sup> Macular degeneration with drusen reduces contrast sensitivity for spatial frequencies above 3 cycles per degree.<sup>38</sup> Cerebral lesions,<sup>39</sup> amblyopia,<sup>40,41</sup> optic neuritis,<sup>42</sup>



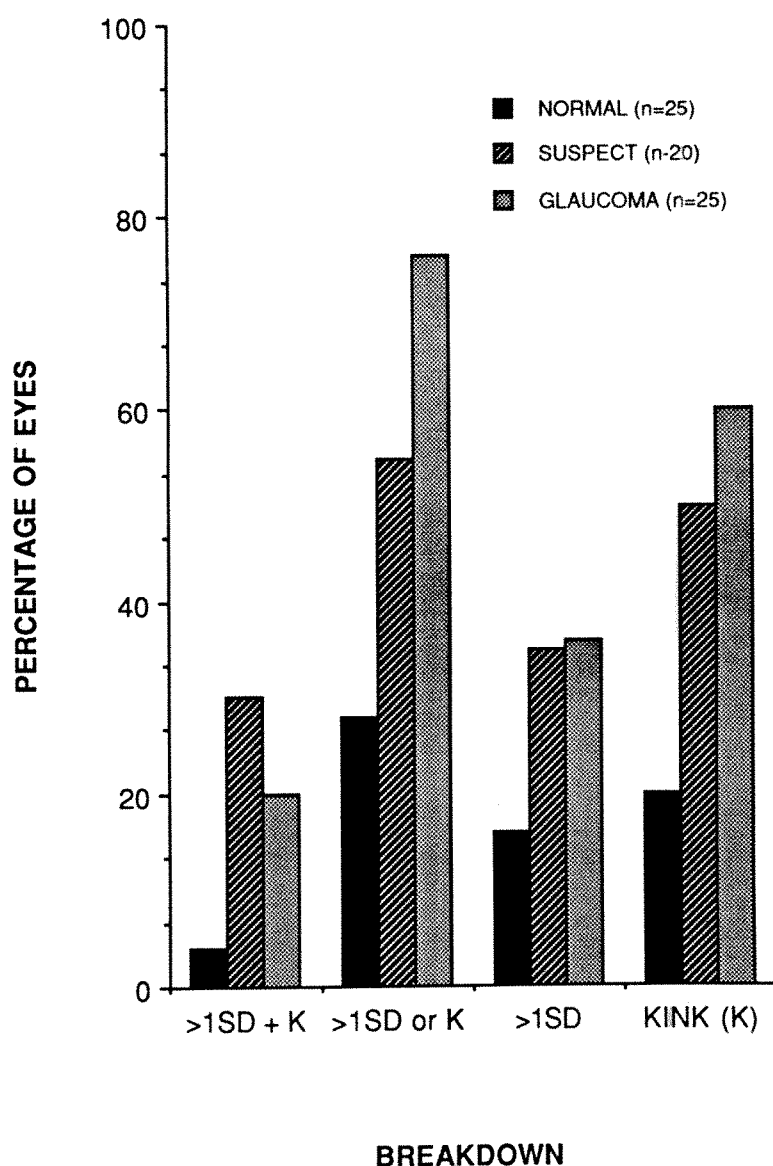


Fig. 6 (Sample, Juang, and Weinreb). The percentage of normal, suspect, and glaucoma eyes in Group 2 that show loss of sensitivity greater than 1 normal standard deviation or a kink.

multiple sclerosis,<sup>43</sup> Alzheimer's disease,<sup>44</sup> and corneal disorders<sup>45</sup> have all been shown to reduce contrast sensitivity. Owsley, Sekuler, and Seisman<sup>35</sup> found that the visual acuity level had a significant effect for spatial frequencies of 2 cycles per degree and above, although our data and those of others<sup>46</sup> have shown that contrast sensitivity can be affected by ocular disease while visual acuity remains intact. Optical factors also affect contrast sensitivity. The natural pupil diameter yielded the best contrast sensitivity, whereas both fixed-miotic or dilated pupils reduced sensitivity.<sup>47</sup> The quality of the retinal image has been shown to be important. Overcorrections of +1.5 diopters resulted in

reduced sensitivity, especially for higher frequency gratings.<sup>48</sup> Finally and most importantly, there is an age-related shift in peak sensitivity from 6 to 3 cycles per degree found by our laboratory (unpublished data) and by others.<sup>36</sup> This is the range where many studies have found glaucoma eyes to be less sensitive. However, the normal eyes in these studies were often significantly younger than those in the glaucoma group, and the reduction at 6 cycles per degree may have been confounded by age.

Controls for age, lens density, visual acuity, pupil size, refraction, ocular disease other than glaucoma, ocular surgical history, and medication should reduce any differences between the

healthy and patient groups to the effects of increased intraocular pressure or primary open-angle glaucoma. With these controls in place, we still found significant differences between healthy eyes and eyes with primary open-angle glaucoma, especially at 12 cycles per degree.

These sensitivity differences were not present for all patients with primary open-angle glaucoma. However, many patients had an abnormal shape to their contrast sensitivity function. Taking the shape into account as well may improve the specificity of the test. Studies generally report only the mean function for the various patient or age groups. The shape of individual contrast sensitivity functions was shown in only one study,<sup>24</sup> in which 21 normal eyes from patients between 50 and 79 years of age were measured out to 12 cycles per degree. None appeared to deviate from the normal function. We did find some older normal eyes with kinks (Fig. 6), but a much higher number of suspect and glaucoma eyes showed this effect. More patients and healthy controls should be studied to determine the prevalence of these kinks.

An accurately measured contrast sensitivity function is a better indicator of a patient's functional ability than Snellen visual acuity or the visual field test, and can be a useful component of a clinical evaluation. However, the current testing procedures for contrast sensitivity and the interpretation of results may only be of limited value for diagnosis and monitoring of primary open-angle glaucoma. Only a small number of eyes with primary open-angle glaucoma do not have coexisting abnormality, such as cataract or age-related macular degeneration. Hence, in most patients with glaucoma, interpretation of contrast sensitivity results are confounded by numerous factors that cannot be easily controlled in clinical practice. Therefore, the results for these eyes should be interpreted with caution.

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# Anterior Uveitis and Hypopyon

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We undertook a study to determine the incidence of hypopyon, as well as the most common anterior uveitis entities with which hypopyon is associated. A total of 216 patients with anterior uveitis were studied. The uveitis was acute in 155. Of the 155 patients, 11 (7.1%) had hypopyon. Nine of the 11 patients with hypopyon were positive for HLA B27. Of these nine, two had Reiter's syndrome and one had ankylosing spondylitis; the other six had no confirmed systemic disease. Of the two patients with hypopyon who were HLA B27-negative, one had mixed connective-tissue vascular disease, and one had idiopathic anterior uveitis. Of the 155 patients with acute anterior uveitis, 62 were HLA B27-positive. Thus, the incidence of hypopyon uveitis among HLA B27-positive patients was 14.5% (nine of 62 patients), whereas the incidence among HLA B27-negative patients was only 2.2% (two of 93 patients). These results suggest that HLA B27-related anterior uveitis is the most common cause of hypopyon uveitis, and that most patients with anterior uveitis associated with hypopyon will test positive for HLA B27. Although these results reflect a referral population, they should be of benefit in the treatment of patients with anterior uveitis.

**A**NTERIOR UVEITIS is the most common form of intraocular inflammation and, when severe, can result in the formation of hypopyon within the anterior chamber. Hypopyon in endogenous anterior uveitis has been related typically to

Behçet's syndrome,<sup>1-3</sup> Hypopyon in association with herpetic keratouveitis,<sup>4,5</sup> Reiter's syndrome, and ankylosing spondylitis<sup>6-8</sup> has sometimes been observed.

We determined the incidence, as well as the most common causes, of hypopyon in patients with acute endogenous anterior uveitis.

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## Patients and Methods

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Medical records of all patients with endogenous anterior uveitis referred to our institution from 1984 to 1990 were reviewed. For each patient, information was obtained regarding the presence or absence of hypopyon on the basis of slit-lamp examination, as well as medical history and results of laboratory investigations.

Laboratory examinations were performed by using a tailored approach (that is, tests were ordered on the basis of the clinical impression of the most likely cause of the uveitis in any given patient), and included any or all of the following: tests for antinuclear antibodies, angiotensin converting enzyme, rheumatoid factor, HLA B27, HLA B5, serologic tests for syphilis, tuberculin skin testing, thoracic radiography, and radiologic examination of the lumbosacral spine.

Patients with concurrent posterior uveitis (retinitis or choroiditis), as well those who had recently undergone ocular surgery or had sustained penetrating trauma to the eye, were excluded.

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## Results

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A total of 216 patients with anterior uveitis were identified. In 155 of these, the condition was classified as acute, endogenous, anterior uveitis, in that the symptoms had an acute onset and the inflammation persisted for less than three months. These patients also met the other criteria for inclusion in this study. Eleven

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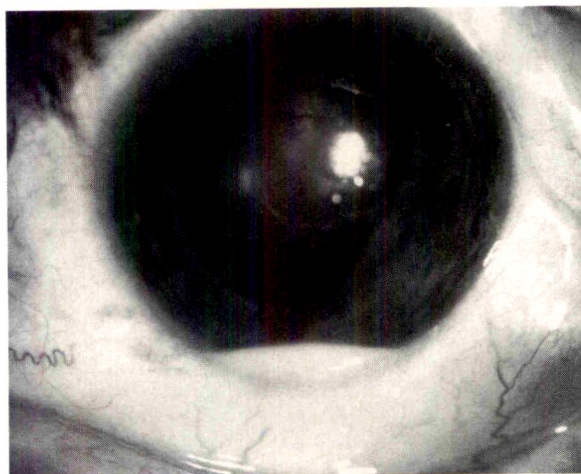
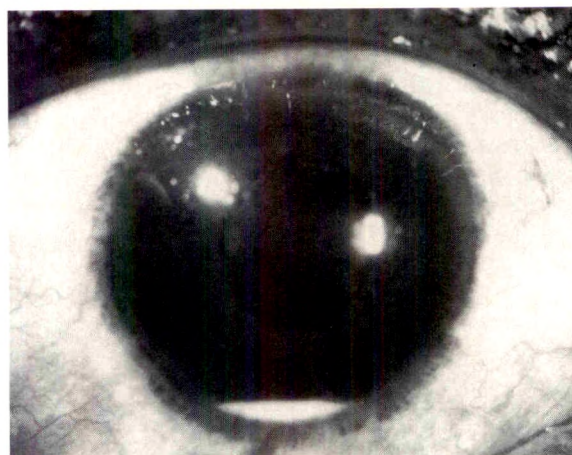
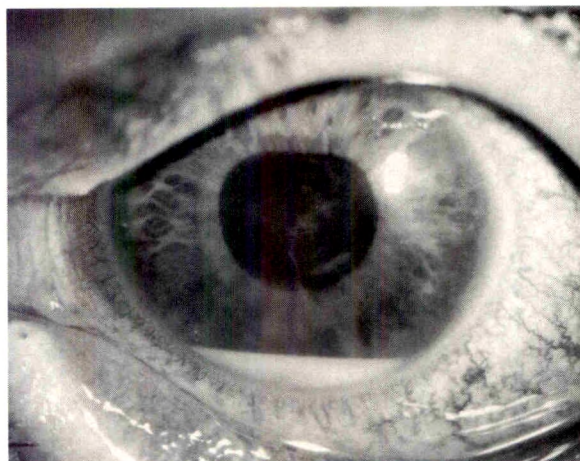


of the 155 patients (7.1%) developed hypopyon. The hypopyon occupied from 5% to 15% of the anterior chamber; in five patients it filled about 5%, in another five it filled 10%, and in the remaining patient it filled about 15% of the anterior chamber.

The characteristics of the patients who developed hypopyon secondary to anterior uveitis are summarized in the Table. The patients ranged in age from 10 to 63 years (mean, 37 years), and there was no apparent predilection for either gender. Overall, a slight majority (55%) of the patients were white, but hypopyon was seen in other races as well (three Orientals, one black, and one Hispanic patient; Figure).

In all cases, the hypopyon was unilateral, and in no cases were there large granulomatous keratic precipitates. The inflammation was acute in all cases and recurrent in eight. The hypopyon developed in the first episode of acute uveitis in only four cases; in the remaining seven, the hypopyon was seen with recurrent episodes of acute anterior uveitis. No patient had a recurrent hypopyon. Four of the 11 patients with hypopyon also had fibrinous membrane formation in the anterior chamber. In two cases, inflammatory cells spilled over pronouncedly into the anterior vitreous humor. Visual acuity at the time of the hypopyon was 20/200 or less in six patients and 20/100 to 20/50 in the other five patients. Ten of the patients were treated with topically administered corticosteroids, topically administered mydriatic agents, and systemic (orally administered) corticosteroids or subtenon depot corticosteroid injections. The remaining patient received topically administered corticosteroids every two hours and mydriatic agents only. Visual acuity in all patients improved by an average of five Snellen lines. After two weeks of treatment, visual acuity was 20/40 or better in ten patients and 20/70 in one patient. In all patients, the hypopyon disappeared within the first ten days of treatment.

In terms of HLA association, nine of the 11 (82%) patients with acute anterior uveitis who developed hypopyon were HLA B27 positive. Two of these HLA B27-positive patients had Reiter's syndrome and one had ankylosing spondylitis; all three of these patients were male. The remaining six HLA B27-positive patients had no documented systemic illness at the time of last examination; four of these patients did complain of lower back pain, but results of radiologic examinations of the lumbosacral region were clinically normal.



**Figure** (D'Alessandro, Forster, and Rao). Hypopyon in HLA B27-related acute anterior uveitis. Top, White patient. Middle, Black patient. Bottom, Oriental patient. Note the associated fibrinous membrane in the top and middle photographs.

Of the HLA B27-negative patients with hypopyon, one had mixed connective-tissue disease and one had idiopathic uveitis; these two patients were white women, aged 63 and 40 years, respectively. In both cases, hypopyon developed during recurrent episodes of uveitis. At the time of the hypopyon, visual acuity in the patient with mixed connective-tissue disease was 20/200 and was 20/70 in the patient with idiopathic anterior uveitis. Both patients were treated with topically administered corticosteroids, mydriatic agents, and systemic (oral) corticosteroids; after two weeks of treatment, visual acuity improved to 20/70 in the patient with mixed connective-tissue disease and to 20/40 in the patient with idiopathic uveitis (the patient with mixed connective-tissue disease also had a history of amblyopia).

Complications were relatively uncommon in this group of patients, but follow-up was not long enough to make a definitive statement regarding long-term sequelae. Three patients developed posterior synechiae and one patient developed bilateral posterior subcapsular cataracts and early band-shaped keratopathy. The cataracts and band-shaped keratopathy developed in a 10-year-old Vietnamese boy (Patient 3), who had a four-year history of recurrent bilateral iridocyclitis. Ankylosing spondylitis was diagnosed in this boy, and had already been diagnosed in his brother. This patient underwent bilateral pars plana lensectomy/vitreotomy, and at last examination, visual acuity was 20/60 in each eye.

Of the 155 patients with acute anterior uveitis, 62 (40%) were HLA B27 positive and 93 were HLA B27 negative, and of the 11 patients with hypopyon, nine were HLA B27 positive and only two were negative. Thus, the incidence of hypopyon among HLA B27-positive patients with acute anterior uveitis was 14.5%, whereas it was only 2.2% among those who were HLA B27 negative. Chi-square analysis of these two groups disclosed significantly increased development of hypopyon in the HLA B27-positive group ( $P < .003$ ). Two patients with Behçet's syndrome and anterior uveitis were included in the group of 155 patients, but these individuals did not develop hypopyon.

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### Discussion

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In this study of patients with anterior uveitis, the most common cause of hypopyon was HLA

B27-related iridocyclitis, accounting for nine of the 11 (82%) cases. However, the incidence of hypopyon among HLA B27-positive patients with acute anterior uveitis was 14.5%. All nine patients had characteristic features of HLA B27-related anterior uveitis; they were young to middle-aged and had acute, unilateral or alternating unilateral, severe episodes of anterior inflammation. Four patients also had associated fibrinous membrane formation in the anterior chamber, but none of the patients had granulomatous keratic precipitates. These findings (including the lack of keratic precipitates) have been described by several authors<sup>7-16</sup> and are typical of HLA B27-related acute anterior uveitis; however, none of these authors found as increased an incidence of hypopyon in association with the anterior uveitis as was observed in our study.

Typically, our patients had been treated initially with intensive (every one to two hours) topically administered corticosteroids for their acute anterior uveitis; however, hypopyon developed despite this treatment, and the majority of the patients required supplemental systemic corticosteroids (generally 60 to 80 mg of prednisone per day) to bring the inflammation under control. The exception was one patient who responded well to intensive topically administered treatment. In all cases, the hypopyon resolved after several days of systemic corticosteroid treatment. None of our patients, including the two with Behçet's syndrome, developed recurrent hypopyon, although this is the typical pattern seen in patients with this syndrome.<sup>1</sup> Two other patients, excluded from this study because they also had evidence of retinal vasculitis, had Behçet's syndrome with the characteristic recurrent hypopyon.

Overall, there did not appear to be a gender predilection among the patients who developed hypopyon. However, among patients who were HLA B27 positive, hypopyon was seen more frequently in men than in women, by a 2:1 ratio. Furthermore, all three patients who had hypopyon associated with an HLA B27-related systemic disease were men.

Of interest in our patients was the wide distribution of cases with respect to race or ethnic origin. HLA B27-related iridocyclitis is typically described as developing in whites. However, only four (44%) of our cases of hypopyon in HLA B27-related acute anterior uveitis developed in white patients; three cases (33%) developed in Oriental patients, one (11%) in a black patient, and one in a Hispanic patient.



Additionally, among the 53 HLA B27-positive patients who did not develop hypopyon, 37 patients (70%) were white, eight patients (15%) were Hispanic, five patients (9%) were Oriental, two patients (4%) were black, and one patient (2%) was Asian Indian.

Our study did not include long-term follow-up, so conclusions could not be drawn regarding the long-term prognosis of these patients. In the short term, however, all but one of our patients maintained good visual acuity with no evidence of cataracts or glaucoma. The one exception was a child (Patient 3), who had a more severe course, with frequent recurrences over several years, and who developed bilateral posterior subcapsular cataracts and early band-shaped keratopathy in one eye. He subsequently underwent bilateral pars plana lensectomy/vitreotomy, and visual acuity at the time of the last visit was 20/60 in each eye.

The data concerning prognosis in HLA B27-related anterior uveitis have been somewhat contradictory. Some authors have reported a good prognosis,<sup>11,15</sup> whereas others have not.<sup>10,13</sup> In a recent report, Rothova and associates<sup>13</sup> suggested that the visual outcome and incidence of complications are probably related to the number of recurrences of the uveitis. Our study of 53 patients with HLA B27-related anterior uveitis without hypopyon seems to support this conclusion. Of the six patients in this group who had a final visual acuity of 20/60 or worse, all had eight or more recur-

rences of acute anterior uveitis and ultimately developed posterior subcapsular cataract or cystoid macular edema.

This study indicates that HLA B27-related iridocyclitis is the most common cause of hypopyon in patients with endogenous anterior uveitis. Whereas HLA B27-related anterior uveitis is seen most frequently in white patients, it can also be seen in patients of other racial groups, including blacks, Hispanics, and Orientals (Table). Patients with hypopyon at initial examination certainly should be questioned about any history of trauma, surgery, intravenous drug abuse, or immunosuppression that may predispose to infectious endophthalmitis, as well as about a history of oral or genital ulcers, arthritis, or dermatologic manifestations, which may be seen in patients with Behçet's syndrome. However, patients also should be questioned regarding a history of lower back pain (ankylosing spondylitis), arthritis or urethritis (Reiter's syndrome), and gastrointestinal abnormalities (inflammatory bowel disease), as any of these entities may exist in patients who are HLA B27 positive. All patients, regardless of race, who had hypopyon at initial examination secondary to anterior uveitis should be examined for the HLA B27 haplotype, and other appropriate investigations (for example, sacroiliac films, rheumatologic evaluation) should be obtained on the basis of the patient's history. Patients may be counseled that, overall, the prognosis for visual acuity is good, but that frequent

TABLE  
CLINICAL CHARACTERISTICS IN HLA B27-POSITIVE AND HLA B27-NEGATIVE PATIENTS WITH ANTERIOR UVEITIS  
AND ASSOCIATED HYPOPYON

CASE NO., AGE (YRS), GENDER	RACE	HLA B27	SYSTEMIC DISEASE	LATERALITY OF UVEITIS	NO. OF RECURRENCES	OCCURRENCE OF HYPOPYON	INITIAL VISUAL ACUITY	CORTICOSTEROID TREATMENT*	LAST VISUAL ACUITY
1, 37, M	Hispanic	+	Reiter's syndrome	Unilateral	5	First episode	20/200	Oral	20/20
2, 53, M	White	+	Reiter's syndrome	Unilateral	2	Recurrence	20/50	Subtenon	20/20
3, 10, M	Oriental	+	Ankylosing spondylitis	Bilateral	8	Recurrence	20/100	Subtenon, oral	20/60
4, 27, M	White	+	None	Unilateral	—	First episode	20/200	Oral	20/20
5, 42, F	White	+	None	Unilateral	—	First episode	20/50	Oral	20/40
6, 29, F	Oriental	+	None	Unilateral	—	First episode	20/400	Oral	20/20
7, 46, M	White	+	None	Unilateral alternating	2	Recurrence	20/50	Topical	20/40
8, 35, M	Black	+	None	Unilateral	3	Recurrence	20/400	Subtenon	20/40
9, 30, F	Oriental	+	None	Unilateral alternating	3	Recurrence	20/400	Oral	20/40
10, 40, F	White	—	None	Bilateral	2	Recurrence	20/70	Oral	20/40
11, 63, F	White	—	Mixed connective-tissue disease	Unilateral	3	Recurrence	20/200	Oral	20/70

\*All patients received cycloplegic eyedrops and topically administered corticosteroids.

recurrences increase the risk of complications and of diminished visual acuity. Longer follow-up is needed on a large number of patients who have uveitis with hypopyon in order to see how their prognosis compares with that of patients with acute anterior uveitis who do not develop hypopyon.

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# Infectious Crystalline Keratopathy Caused by *Candida albicans*

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Two patients developed corneal opacities resembling infectious crystalline keratopathy. Predisposing factors included a recent corneal transplant with suture replacement in one patient and postradiation keratoconjunctivitis with disposable therapeutic contact-lens wear in the other patient. Both patients were using a topically applied corticosteroid and an aminoglycoside antimicrobial. Smears of corneal scrapings showed numerous yeasts without inflammatory cells. Culturing yielded *Candida albicans* and *Staphylococcus haemolyticus* in the first case and *C. albicans* and *S. epidermidis* in the second case. Combined antifungal and antimicrobial therapy, with initial withdrawal of corticosteroid use, was effective. The microbial cause of pauci-inflammatory keratitis includes not only viridans streptococci and other bacteria but fungi as well.

**I**NFECTIOUS CRYSTALLINE keratopathy is a chronic corneal infection characterized by intrastromal arborescent opacities.<sup>1,2</sup> These branching changes are collections of bacterial colonies without inflammation. Predisposing factors include topically applied corticosteroid use, corneal transplantation, and previous corneal disease. Viridans streptococci account for most cases,<sup>3</sup> but other bacteria such as *Staphylococcus epidermidis* have also caused intrastromal crystalline changes.<sup>4,5</sup> Fungi typically cause suppurative keratitis, sometimes with filamentous borders that mimic infectious crystalline keratopathy.<sup>6</sup> One previous report identified *Candida tropicalis* from crystalline infiltrates after keratoplasty.<sup>6</sup> We studied two cases in which *C. albicans* and *Staphylococcus* species were isolated from similar opacities.

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## Case Reports

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### Case 1

A 74-year-old woman underwent penetrating keratoplasty for Fuchs' corneal dystrophy. Four months after surgery, loose interrupted sutures were replaced along the inferotemporal graft-host junction, and she continued topical application of tobramycin-dexamethasone solution. Over the next three months, nonsuppurative infiltrates formed around several sutures, prompting selective suture removal. These opacities became more like crystalline with arborescent extensions into the peripheral graft (Fig. 1, top left and right), and partial wound dehiscence developed. Corneal scrapings of the stromal infiltrates showed many yeasts without inflammatory cells (Fig. 1, bottom left). Treatment was begun with topical application of amphotericin B 0.15% every half hour and oral administration of ketoconazole, 200 mg twice daily; topical application of cefazolin 5% was added the next day. Culturing yielded *C. albicans* and *S. haemolyticus*. Minimal inhibitory concentrations of the *C. albicans* isolate were  $> 8 \mu\text{g/ml}$  for amphotericin B and  $0.25 \mu\text{g/ml}$  for ketoconazole. Minimal inhibitory concentrations (and minimal lethal concentrations) for *S. haemolyticus* were  $16 \mu\text{g/ml}$  ( $16 \mu\text{g/ml}$ ) for penicillin G,  $> 8 \mu\text{g/ml}$  for methicillin,  $1 \mu\text{g/ml}$  ( $1 \mu\text{g/ml}$ ) for vancomycin, and  $> 16 \mu\text{g/ml}$  for gentamicin. Antimicrobial treatment was gradually tapered and discontinued after five weeks. Visual acuity was limited to 20/60 because of mild graft edema and cataract that improved after regrafting and cataract surgery.

### Case 2

A 59-year-old man developed chronic keratoconjunctivitis sicca with conjunctival keratinization after radiotherapy four years previously for maxillary sinus carcinoma. He had been using disposable soft contact lenses and topically applied gentamicin and dexamethasone solutions when he developed multiple stromal crystalline opacities (Fig. 2). Smears of corneal

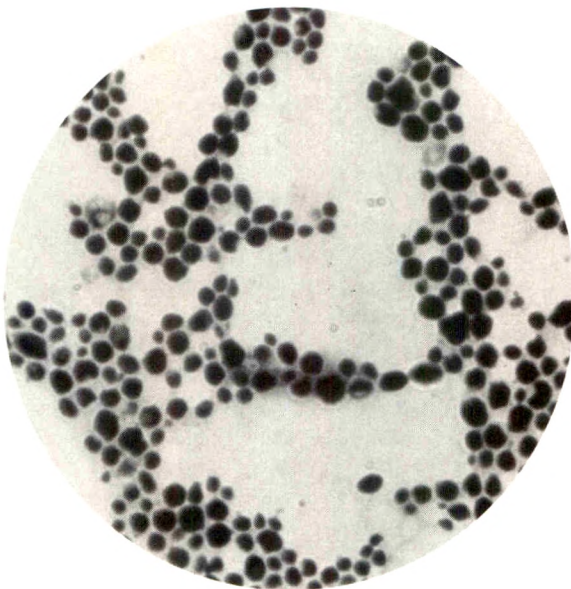
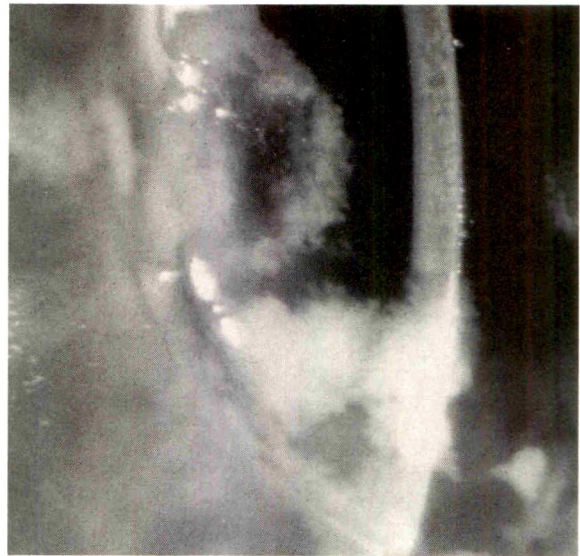
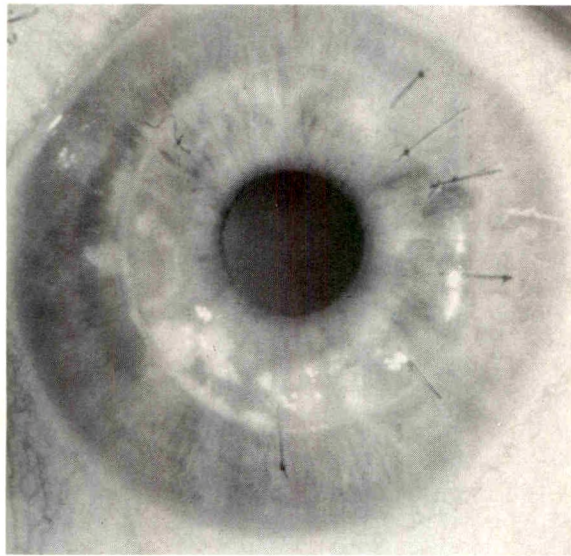


Fig. 1 (Wilhelmus and Robinson). Case 1. Top left, Corneal stromal opacities associated with previous suture tracks in the graft-host junction. Top right, Higher magnification shows crystalline changes in the peripheral corneal transplant. Bottom left, Gram-stained smear of corneal scrapings shows many yeasts but no leukocytes ( $\times 630$ ).

scrapings showed budding yeasts and gram-positive cocci. Initial treatment included a penicillin G-soaked collagen shield. Topical application of cefazolin 5% and amphotericin B 0.15% solutions was begun along with oral administration of ketoconazole. Culturing yielded *C. albicans* and *S. epidermidis*. Minimal inhibitory concentrations (and minimal lethal concentrations) of *C. albicans* were 0.5  $\mu\text{g}/\text{ml}$  (1  $\mu\text{g}/\text{ml}$ ) for amphotericin B and  $\leq 0.125$   $\mu\text{g}/\text{ml}$  (2  $\mu\text{g}/\text{ml}$ ) for ketoconazole. Minimal inhibitory concentrations for *S. epidermidis* were  $> 4$   $\mu\text{g}/\text{ml}$  for penicillin G,  $> 32$   $\mu\text{g}/\text{ml}$  for methicillin, 2  $\mu\text{g}/\text{ml}$  for vancomycin, and  $> 32$   $\mu\text{g}/\text{ml}$  for

gentamicin. Treatment was changed from cefazolin to vancomycin 2.5%, and the collagen shield was replaced. Antimicrobial therapy was gradually tapered and discontinued after three weeks, with subsequent corneal reepithelialization. Visual acuity was limited to light perception because of neovascular glaucoma.

### Discussion

The finding of multiple white opacities with borders resembling needles within the anterior



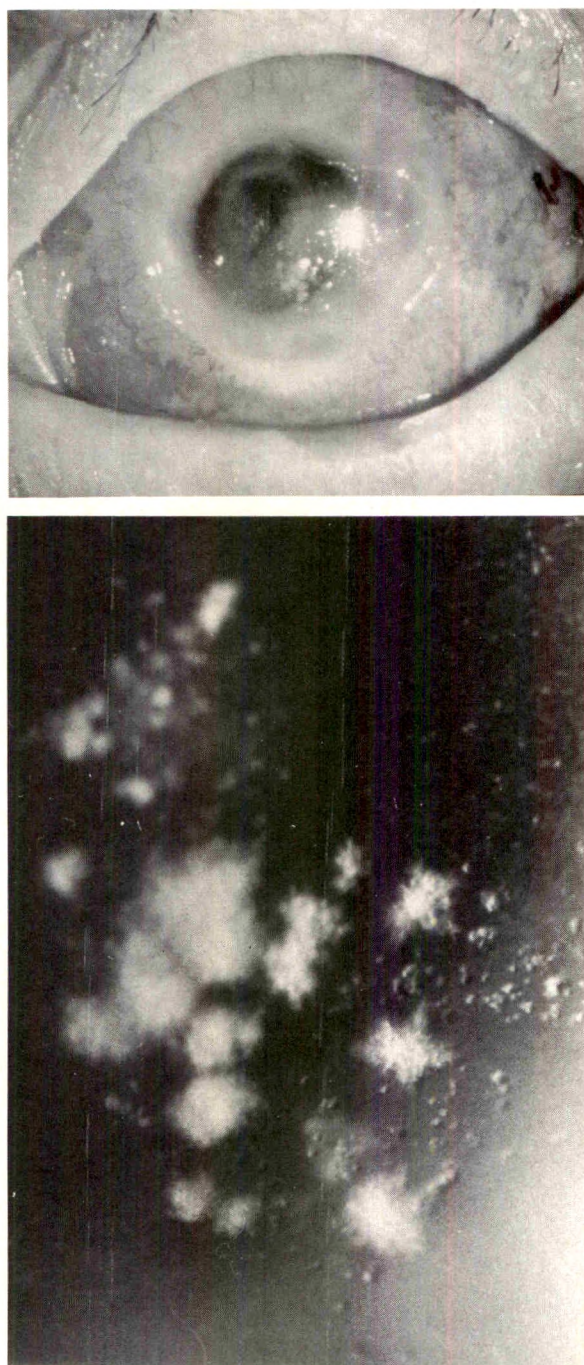


Fig. 2 (Wilhelmus and Robinson). Case 2. Top, Central cluster of corneal crystalline opacities in a patient with postradiation keratoconjunctivitis. Bottom, Higher magnification shows discrete snowflake appearance of anterior stromal changes.

stroma in these two patients suggested infectious crystalline keratopathy. The clinical appearance of the focal branching network is presumably caused by microbial colonies growing between stromal lamellae.

Smears of corneal scrapings of both cases showed numerous yeasts without inflammatory cells. Use of a topically applied corticosteroid probably accounted for the initial lack of corneal suppuration because stromal cellular infiltration subsequently developed when the corticosteroid was discontinued. Other anatomic or microbiologic mechanisms may also limit an inflammatory response.<sup>7</sup>

These patients were using a corticosteroid and an aminoglycoside antimicrobial, both of which have been suggested to predispose to oculomycosis.<sup>8</sup> Topical application of antimicrobials eliminates common conjunctival bacteria that compete with yeasts, and corticosteroids can favor fungal growth by immunosuppressant and anti-inflammatory effects and possibly by direct actions on *C. albicans*.<sup>9</sup> These agents enhance fungal proliferation of the conjunctiva<sup>10</sup> and potentiate experimental keratitis caused by *Candida* organisms.<sup>9</sup> Even so, the extent to which these drugs predispose to fungal keratitis is difficult to determine. For example, it is unclear whether dexamethasone does<sup>11,12</sup> or does not<sup>13</sup> facilitate *C. albicans* corneal infection and does<sup>14</sup> or does not<sup>15</sup> promote epithelial adherence by *C. albicans*. Probably more important in pathogenesis are the reasons why these drugs are being used. To illustrate, a prophylactic antimicrobial is sometimes used for a corneal epithelial defect that, in turn, favors *C. albicans* adherence.<sup>16</sup>

Other risk factors predisposing to microbial keratitis in these patients included corneal transplantation and therapeutic soft contact lens wear. Suture tracks and persistent epithelial defects permit a portal of entry for microorganisms. In a study of corneal infections developing more than one month after keratoplasty, *C. albicans* and staphylococci were the most commonly isolated microorganisms.<sup>17</sup> Changes resembling crystalline in the peripheral corneal graft have previously been associated with *C. tropicalis* infection,<sup>6</sup> similar to the clinical appearance of the patient described in Case 1.

Yeasts are infrequently part of the usual ocular flora,<sup>9,18</sup> even with soft contact lenses,<sup>19</sup> but fungal keratitis can be a complication of contact-lens wear.<sup>20</sup> Therapeutic, rather than cosmetic, contact lenses seem more likely to be associated with infections caused by *Candida* organisms,<sup>20</sup> perhaps because tear proteins enhance yeast adherence to the lens surface.<sup>21</sup> The snowflake pattern associated with a disposable bandage lens in Case 2 mirrors similar deposits sometimes seen on soft contact lenses.

Corneas with keratitis caused by *Candida* organisms are frequently co-infected with *S. aureus* or *Streptococcus* species, suggesting a synergistic interaction between yeasts and bacteria. *Candida albicans* enhances proliferation of *S. aureus* by providing some protection or a favorable growth environment.<sup>22,23</sup>

As the spectrum of responsible microorganisms increases, laboratory evaluation is needed to guide management of infectious crystalline keratopathy rather than initiating treatment for presumptive streptococcal infection.<sup>6</sup> Culturing of corneal scrapings or biopsy material, or both, should include media for both bacterial and fungal isolation.

#### ACKNOWLEDGMENT

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# The Effect of Corneal Hypesthesia on the Duration of Proparacaine Anesthetic Eyedrops

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Jayne S. Weiss, M.D., and Matthew B. Goren, M.D.

The duration of action of proparacaine is known in the normal cornea but not in the hypesthetic cornea. To determine this, we examined both eyes in seven patients with documented unilateral corneal hypesthesia associated with inactive herpetic disease. Cochet-Bonnet measurements were made in both eyes before and at two- to five-minute intervals after the instillation of one drop of 0.5% proparacaine until baseline corneal sensitivity levels were again achieved. Mean recovery time was 34.86 minutes in eyes with normal corneal sensitivity, compared to 45.43 minutes in hypesthetic corneas. In all patients, the recovery time was remarkably longer in the hypesthetic eye than it was in the normal fellow eye. These data demonstrate the need to wait up to one hour after the instillation of proparacaine in eyes suspected of having corneal hypesthesia if corneal sensitivity is to be determined accurately. Additionally, the duration of action of topically instilled anesthetic may be a useful method of discovering subtle differences in corneal sensitivity.

**T**HE QUANTIFICATION of corneal sensitivity is important in the diagnosis, monitoring, and prognosis of corneal and systemic disease with ciliary nerve involvement.<sup>1-7</sup> The ophthalmologist may wish to determine corneal sensitivity in an eye that has already been subjected to eyedrops containing proparacaine. The dura-

tion of action of proparacaine eyedrops is known in the normal cornea<sup>8-11</sup> but not in the hypesthetic cornea. We conducted this study to determine the effect of corneal hypesthesia on the duration of action of 0.5% proparacaine eyedrops.

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## Material and Methods

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Both eyes in seven patients with unilateral corneal hypesthesia from herpetic disease (five with herpes zoster and two with herpes simplex) were studied. The unaffected eyes served as controls. Six men and one woman (mean age, 61 years; range, 30 to 80 years) were examined (Table). No patient had had previous ocular surgery or was taking any ophthalmic medication known to affect corneal sensitivity. No patient had any evidence of active corneal disease at the time of the study.

Corneal sensitivity was measured as previously described<sup>2-6,8,12</sup> with the Cochet-Bonnet esthesiometer<sup>13</sup>, which was modeled after the instrument devised by Boberg-Ans.<sup>14</sup> Briefly, the instrument consists of a cylinder encasing a 0.12-mm-diameter nylon filament, the length of which can be varied from 6.0 to 0.5 cm. The lengths correspond to pressures of 11 to 200 mg/mm<sup>2</sup> when touched against the cornea, thus allowing quantification of corneal sensitivity. The esthesiometer was mounted on a slit lamp, the patient was instructed to fixate on a distant point, and the filament was set to its maximal length (most sensitive level). The filament was slowly brought toward a point (2 mm from the 6:00 position of the corneoscleral limbus) until corneal contact was achieved, which caused the nylon filament to deflect approximately 5 degrees. This was repeated five times in succession for each filament length. A positive response (ability to perceive the stimulus) was recorded if the patient made a verbal indication of contact or an objective reaction, that is, a blink or withdrawal movement, in three or

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TABLE  
PATIENT CHARACTERISTICS

CASE NO., AGE (YRS), GENDER	EYE	DIAGNOSIS	DURATION OF MAXIMAL EFFECT (MIN)	TOTAL DURATION OF ACTION (MIN)
1, 30, M	Right eye	Control	5	22
	Left eye	Herpes simplex	5	44
2, 72, M	Right eye	Control	10	34
	Left eye	Herpes zoster	10	38
3, 62, M	Right eye	Control	10	24
	Left eye	Herpes zoster	15	32
4, 53, F	Right eye	Control	12	32
	Left eye	Herpes zoster	24	52
5, 80, M	Right eye	Control	15	26
	Left eye	Herpes zoster	22	36
6, 61, M	Right eye	Herpes zoster	22	68
	Left eye	Control	10	62
7, 69, M	Right eye	Herpes simplex	28	48
	Left eye	Control	20	42

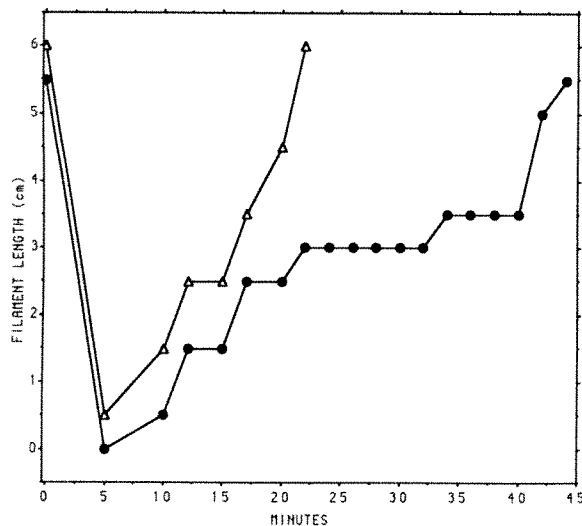
more of the five trials. If there was no sensation, the filament length was decreased by 0.5 cm and testing was performed until a positive response was elicited. The maximal filament length at which a positive response was observed was recorded as the threshold of corneal sensitivity for that eye. All measurements were recorded by a single observer.

Corneal sensitivity was measured in both eyes before and at two- to five-minute intervals after the instillation of one drop (50  $\mu$ l) of 0.5% proparacaine until baseline corneal sensitivity

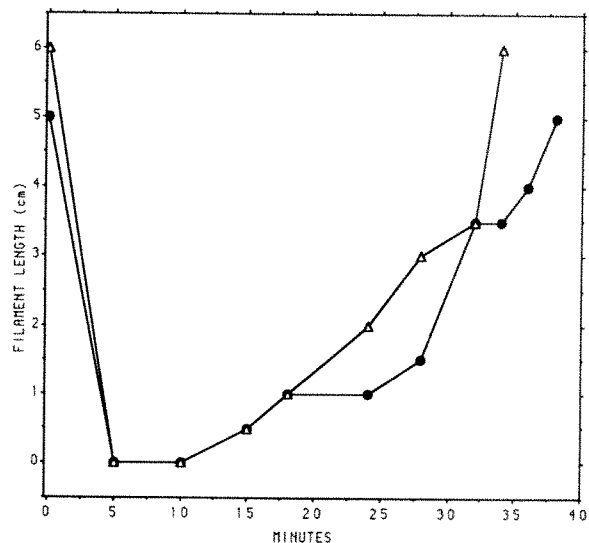
levels were again achieved. Corneal sensitivity was then plotted for each eye as a function of time (Figs. 1 through 7). Statistical comparison was performed by using the paired *t*-test.

## Results

All control eyes except one (Case 5) had the maximal baseline corneal sensitivity that could

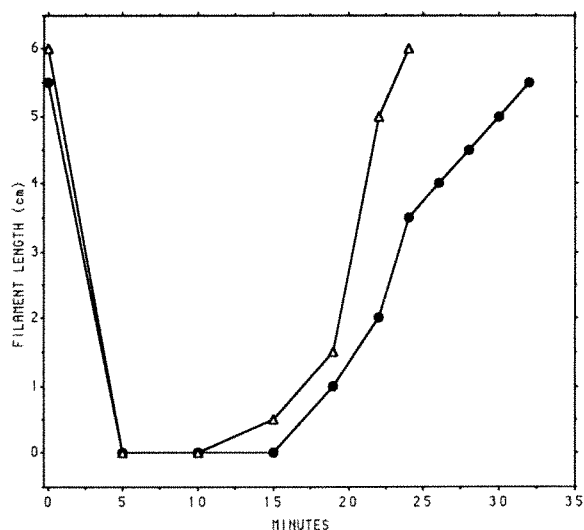


**Fig. 1** (Weiss and Goren). Case 1. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes simplex-affected eye).

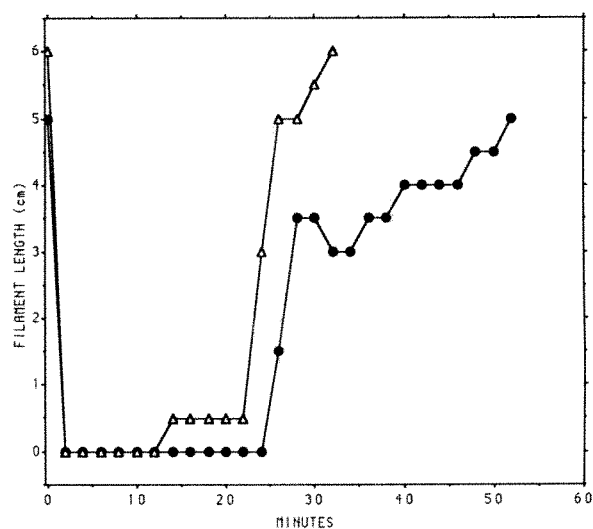


**Fig. 2** (Weiss and Goren). Case 2. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes zoster-affected eye).





**Fig. 3** (Weiss and Goren). Case 3. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes zoster-affected eye).

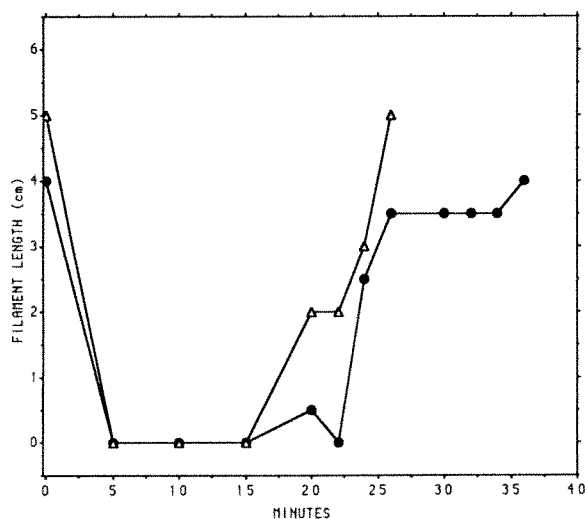


**Fig. 4** (Weiss and Goren). Case 4. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes zoster-affected eye).

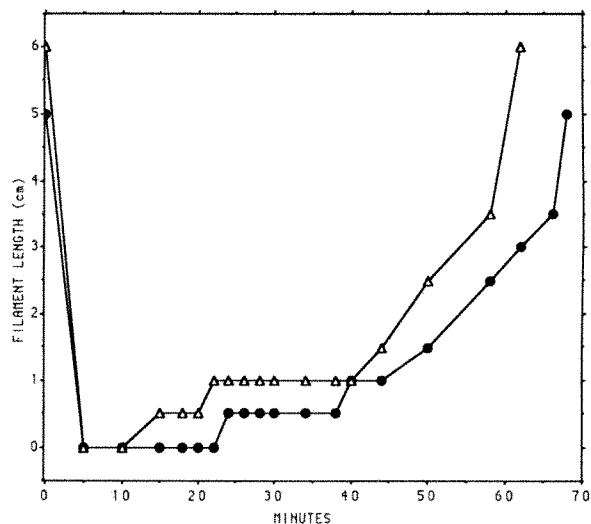
be measured with the Cochet-Bonnet esthesiometer (Figs. 1 through 7). Mean baseline threshold of corneal sensitivity was 5.85 cm in control eyes, in contrast to 4.78 cm in affected eyes. In each case, the affected eye had a lower baseline corneal sensitivity than did the control eye. The complete recovery time for the control eyes averaged 34.86 minutes (standard deviation, 14.55; range, 22 to 64 minutes) compared to 45.43 minutes (standard deviation, 12.15;

range, 32 to 68 minutes) for hypesthetic eyes. In every case, the duration of action of proparacaine was significantly longer in the hypesthetic eye than it was in the normal eye ( $P = .005$ ).

The duration of maximal effect of proparacaine in control eyes averaged 11.71 minutes (standard deviation, 4.72; range, ten to 26 minutes) compared to 18.0 minutes (standard deviation, 8.27; range, ten to 28 minutes) for hypesthetic corneas. These differences were also



**Fig. 5** (Weiss and Goren). Case 5. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes zoster-affected eye).



**Fig. 6** (Weiss and Goren). Case 6. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes zoster-affected eye).

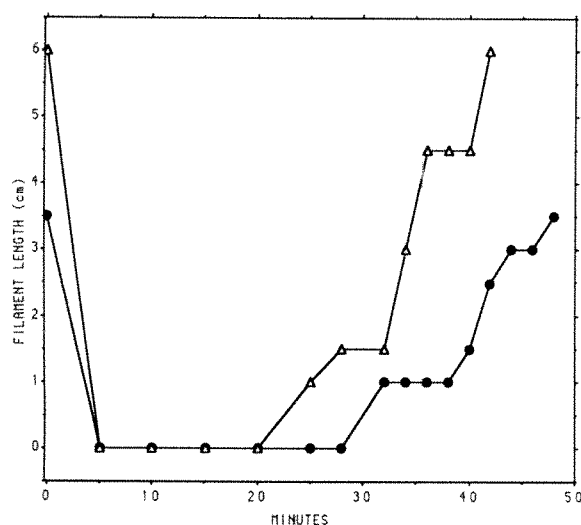


Fig. 7 (Weiss and Goren). Case 7. Corneal sensation curve plotted against time (solid line with triangles, control; solid line with circles, herpes simplex-affected eye).

significant ( $P = .01$ ). Although there were two patients in whom the durations of maximal effect were the same for both eyes (Cases 1 and 2), there were no patients in whom the duration was longer in the control eye than it was in the affected eye. A difference in duration of maximal effect may have been masked in Cases 1 and 2 in the first five minutes after instillation before sensitivity was measured.

### Discussion

This study demonstrates that the total duration of action and the duration of maximal effect of 0.5% proparacaine are prolonged when applied to hypesthetic corneas associated with inactive herpetic keratitis. Most studies have found the mean recovery time of eyes subjected to 0.5% proparacaine to range from 14 to 20 minutes<sup>9-11</sup> and may be as long as 60 minutes.<sup>8</sup> We found a mean recovery time of 34.86 minutes among normal eyes and of 45.43 minutes among affected eyes. Although the normal eyes in this study had recovery times within the range previously described, the recovery times were slightly longer than the usual duration of action of 0.5% proparacaine eyedrops. We could isolate no factors to explain why the normal eyes in our study recovered in this manner. Numerous factors may influence sensitivity in the normal cornea including diurnal

variation, eye color, temperature, humidity, age, the presence of an arcus, menstruation, pregnancy, and corneal eccentricity with the highest sensitivities recorded centrally.<sup>3,4</sup>

Numerous methods have been devised to quantitate corneal sensitivity.<sup>2,3,12,15-20</sup> The Cochet-Bonnet esthesiometer remains the most widely used instrument but its use still includes drawbacks such as variability with changes in temperature and humidity, inadvertent changes in the shape of the nylon filament, and the subjective problem of the blink reflex.<sup>2,3,16</sup> We attempted to minimize these errors by testing all patients under similar environmental conditions in the same examining room during the same season at the same time of day. We also examined the nylon filament for defects after each use and used a corneal focus away from the visual axis to minimize the blink reflex when testing.<sup>12</sup>

There are several possibilities that may explain the prolonged effect of proparacaine in hypesthetic corneas. The bioavailability of eyedrops is generally poor because of nasolacrimal duct drainage and tear turnover. Corneal anesthesia in rabbits has been shown to decrease tear production and enhance the bioavailability of topically instilled drugs through less tear dilution.<sup>21</sup> It is possible that the baseline level of corneal hypesthesia in our patients decreased basal tear secretion sufficiently to enhance the absorption of proparacaine. We did not attempt to quantify basal tear secretion in our patients.

Herpetic keratitis may alter the corneal tissues sufficiently to allow greater diffusion and bioavailability of the anesthetic. Proparacaine causes electron microscopically visible changes in the corneal epithelium.<sup>22</sup> This may increase absorption considerably to augment anesthesia in a cornea that is already compromised.

Surface charge density<sup>23</sup> and protein binding<sup>24</sup> may also affect corneal drug absorption. We are unaware of reports linking those factors to herpetic corneal disease.

Finally, enzymatic inactivation of proparacaine by corneal esterases may affect the duration of drug action.<sup>24</sup> Prolongation of activity can be experimentally achieved by inhibiting hydrolysis of the anesthetic's ester linkage. Studies in rabbits, however, show no correlation between the duration of anesthesia and in vitro hydrolytic activity.

On the basis of the results of this study, we recommend waiting up to one hour after the instillation of 0.5% proparacaine eyedrops in



eyes suspected of having corneal hypesthesia if corneal sensitivity is to be determined accurately. Additionally, comparison of the durations of action of 0.5% proparacaine eyedrops of each eye of a patient may be used as a challenge test in an attempt to detect subtle differences in corneal sensitivity.

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# Conjunctival Ophthalmomyiasis Caused by the Sheep Nasal Botfly (*Oestrus ovis*)

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James A. Cameron, M.D., Nader M. Shoukrey, Ph.D., and Abdullah A. Al-Garni, M.D.

Three patients had conjunctival ophthalmomyiasis caused by the ovine nasal botfly. All patients had a sudden onset of redness, tearing, and foreign-body sensation of the affected eye. One to nine *Oestrus ovis* first-instar larvae were removed from the bulbar or palpebral conjunctiva of each patient. Symptoms and clinical signs resolved after mechanical removal of the larvae. Specific taxonomic diagnosis of *O. ovis* larvae was determined on the basis of characteristic conformation of the terminal end of the larval caudal segment as seen by use of light microscopy.

**H**UMAN MYIASIS is a disease resulting from the infestation of parts of the body by certain fly maggots (larvae). Myiasis of the eye or ocular adnexa is referred to as ophthalmomyiasis. On the basis of the site of infestation, ophthalmomyiasis may be classified as external, internal, or orbital. External ophthalmomyiasis results from the deposition of larvae on the conjunctiva or eyelids.<sup>1</sup> Internal ophthalmomyiasis<sup>2-4</sup> develops when the larvae penetrate the globe. Once through the sclera, the larvae may be visible in the subretinal space and sometimes in the vitreous cavity.<sup>4</sup> Orbital myiasis, the least common form of ophthalmomyiasis, results from invasion of the orbit by larvae, causing destruction of orbital contents with severe ocular damage.<sup>5</sup>

Conjunctival ophthalmomyiasis in humans is commonly caused by the ovine nasal botfly, *Oestrus ovis*,<sup>6,9</sup> and the Russian botfly, *Rhinoestrus purpureus*.<sup>10</sup> Larvae of *O. ovis* are well-known parasites of the nasal cavities and paranasal sinuses of domestic sheep and goats and are found in most sheep-farming communi-

ties.<sup>11</sup> Cases of conjunctival ophthalmomyiasis caused by the larvae of *O. ovis* have been reported from Africa,<sup>12</sup> the Middle East,<sup>8</sup> U.S.S.R.,<sup>13</sup> Europe,<sup>13</sup> and the United States.<sup>6,7</sup>

Three cases of conjunctival ophthalmomyiasis caused by the *O. ovis* larvae were studied. The three patients were admitted to the emergency room at King Khaled Eye Specialist Hospital within an eight-month period. The specific taxonomic diagnosis of *O. ovis* larvae was determined on the basis of characteristic light microscopy findings.

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## Case Reports

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### Case 1

A 30-year-old man was admitted to the emergency room on Oct. 20, 1989. He complained of foreign-body sensation, redness, and tearing of his right eye for three hours. Symptoms started after the patient had slaughtered one of his sheep.

On examination, visual acuity was R.E.: 20/25 and L.E.: 20/20. The right conjunctiva was hyperemic with multiple small subconjunctival hemorrhages. The cornea had a punctate keratitis. Nine mobile larvae, approximately 1 mm in length, were on the bulbar and palpebral conjunctivae. The larvae moved rapidly across the conjunctivae, away from the slit-lamp light. They attempted to attach themselves to the conjunctiva with their buccal hooks. After anesthetic was applied topically, the larvae were removed with forceps. Small conjunctival hemorrhages were sometimes observed where the larvae had been removed. After mechanical removal and treatment with antibiotic drops and ointment, symptoms and clinical signs resolved within one week.

### Case 2

A 61-year-old man was admitted to the emergency room on Oct. 29, 1989. He complained of

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redness, tearing, and itching of his right eye for the preceding four days. He noticed the onset of symptoms after he shoveled food for his sheep.

On examination, visual acuity was R.E.: 20/40 and L.E.: 20/100. Immature cataracts were present in both eyes. There was mild injection of the right conjunctiva with a papillary reaction of the palpebral conjunctiva. A motile larva (Figs. 1 and 2) was removed with resulting resolution of symptoms and clinical signs.

### Case 3

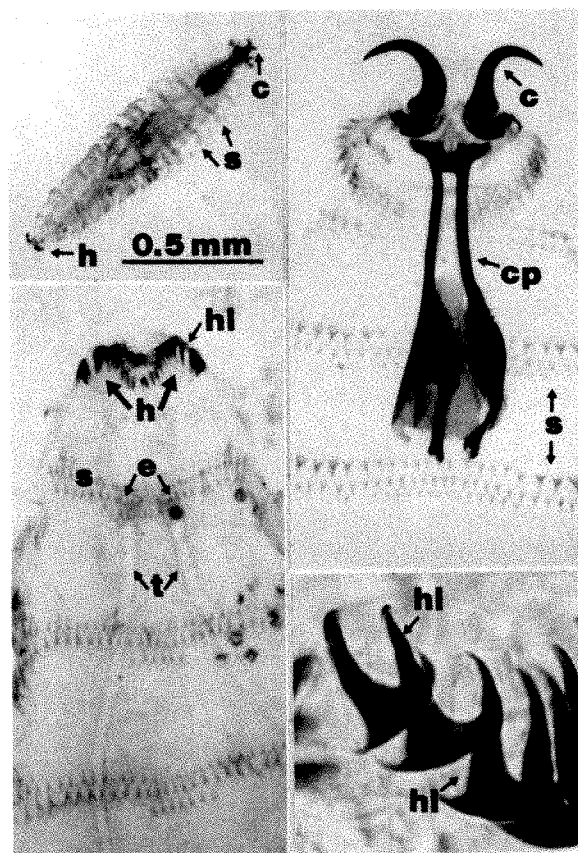
A 25-year-old man was admitted to the emergency room on May 6, 1990, because of a one-day history of redness, tearing, and foreign-body sensation in his right eye. He had been on a farm on the same day the symptoms had started.

On examination, visual acuity was 20/25 in both eyes. Three motile larvae were visible on the palpebral and bulbar conjunctivae of his right eye. The cornea had a mild punctate keratitis. Larvae were mechanically removed after application of topical anesthetic. Antibiotic drops and ointment were given to the patient and symptoms and clinical signs resolved within 24 hours.

**Entomologic findings**—Maggots removed from the patients' conjunctivae were transferred into 10% buffered formalin for preservation. Light microscopic examination identified the preserved maggots as first-instar larvae of the ovine nasal botfly, *O. ovis*, of the order Diptera, family Oestridae. The maggots were identified in accordance with taxonomic guidelines given



**Fig. 1** (Cameron, Shoukrey, and Al-Garni). Case 2. First-instar larva of the ovine botfly, *Oestrus ovis*, on the upper palpebral conjunctiva. Note the mouth claws (c), portions of the intersegmental spine bands (s), and the terminal double hump (h).



**Fig. 2** (Cameron, Shoukrey, and Al-Garni). Case 2. Top left, Ventral view of first-instar larva from conjunctiva showing anterior mouth claws (c), ventral intersegmental spine bands (s), and terminal double hump (h) in the caudal segment. Top right, Magnification of the mouth claws (c) and their connection with the cephalopharyngeal skeleton (cp). Note the arrangement of the intersegmental spine bands (s). Bottom left, Magnification of the terminal double hump (h) showing the arrangement of 12 hooklets (hl) on each hump. Note the level of exit (e) of the terminal tracheal trunks (t) in relation to the terminal intersegmental spine band (s). Bottom right, Magnification of part of the series of hooklets (hl) on the terminal double hump.

by Krümmel and Brauns<sup>14</sup> and Sergent.<sup>15</sup> The removed larvae, translucent and white in color, measured about 1.1 mm in length (Fig. 2, Top left). Each body consisted of an anterior end equipped with a pair of well-developed, horn-like, dark-colored mouth claws (Fig. 2, Top right). The larvae also had 11 abdominal segments, each having a ventral belt of minute dark spines. There were no posterior spiracular plates and the two major caudal tracheal trunks exited directly in the plane with the ventral

spine belt of the caudal segment (Fig. 2, Bottom right). Differential diagnosis in favor of *O. ovis* larvae against the taxonomically similar *R. purpureus* larvae was determined on the basis of conformation of the terminal end of the caudal segment. In *O. ovis* larvae, the caudal segment has two terminal bulges, each carrying 12 hooklets (Fig. 2); the caudal segment of *R. purpureus* has a single terminal hump carrying 11 thornlets.

### Discussion

The ovine botfly, *O. ovis*, is a widely distributed species. Adult flies are slightly larger than the common housefly, *Musca domestica*. Females hatch their eggs while the eggs are still in the vagina, and maggots are then deposited by the viviparous female in the nostrils of sheep, goats, and related wild hosts in early summer to late autumn. First-instar larvae, commonly known as sheep bot, work their way into the nasal and frontal sinuses and attach themselves to the mucous membranes. Maturation to the second- and third-instar larvae takes place in the sinuses. The mature larvae then wiggle out of the nostrils, or are sneezed out by the host, fall to the ground, and pupate. Adult flies emerge from the pupal period after three to six weeks and may live for as long as one month.

The typical patient with conjunctival ophthalmomyiasis as a result of *O. ovis* larvae is one who has had a close association with sheep or goats in early summer to late fall. The patient may report being struck in the eye by an insect or a small foreign object, with pain and inflammation developing a few hours later. Deposition of larvae on the eyelid, conjunctiva, or both, may be by direct contact between the gravid female *O. ovis* and humans.<sup>16</sup> Alternatively, a jet of larvae is ejected in a milky fluid from the female while she is in flight, landing in or adjacent to the eye.<sup>13</sup> Because human beings are not the normal hosts of this parasite, the deposited larvae do not progress beyond the first stage. The larvae will eventually die within ten days, with resolution of symptoms.<sup>11</sup>

Symptoms in conjunctival ophthalmomyiasis in humans are related to the mobile foreign body and the inflammatory response induced by the larvae. A punctate keratitis may be seen, as a result of the larvae moving across the cornea. Small conjunctival hemorrhages may be apparent at sites where the larva clings with its mouth claws. Inflammatory clinical signs

may be sufficiently intense as to mimic orbital cellulitis.<sup>8</sup>

A similar, yet much more dangerous form of conjunctival ophthalmomyiasis in humans is caused by the Russian botfly, *R. purpureus*. The larvae of this fly species are parasitic in the nasal passages of equines in southern Europe, Asia Minor, and Africa.<sup>17</sup> The fly sometimes deposits larvae in or near the eye in humans. Larval development of *R. purpureus*, as with *O. ovis*, does not progress beyond the first stage. However, if left alone, *R. purpureus* larvae may burrow into the eye and cause loss of vision.<sup>16</sup> It is therefore imperative that such cases are recognized at an early stage when symptoms are still mild and a cure by removal of the parasite is easily accomplished.

The detection of the larvae in the conjunctiva is aided first, by the dark mouth claws by which the parasite clings to the conjunctiva and second, by the active vermiform movements of the slender elongated body of the parasite against the red and swollen conjunctiva. Double eversion of the eyelid may be necessary to detect larvae in the conjunctival fornix. Treatment consists of slowing the movement of and then removing the larvae after applying topical anesthetic. The use of cocaine eyedrops paralyzes the movements or loosens the hold of the larvae so that the larvae can be more easily removed with forceps.<sup>13</sup>

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#### OPHTHALMIC MINIATURE

Removing his spectacles from his ears, he fumbled distractedly with his shirt front, looking for I could not imagine what, until I realized that it was the fat end of the necktie on which he was accustomed to polish his lenses. But an awkwardly assembled black bow tie provides no such conveniences, so he used his silk handkerchief from his pocket instead.

"If I regret anything at all, it's the way we wasted our time and skills. All the false alleys, and bogus friends, the misapplication of our energies. All the delusions we had about who we were." He replaced his spectacles and, as I fancied, turned his smile upon myself.

John LeCarré, *The Secret Pilgrim*  
New York, Alfred A. Knopf, 1990, p. 12-13

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## PERSPECTIVES

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### Human Immunodeficiency Virus Disease Epidemiology and Nosocomial Infection

Rafael Ortiz, M.D., and Thomas M. Aaberg, M.D.

Although the ophthalmic literature contains abundant information on ocular manifestations of human immunodeficiency virus disease, information is relatively scarce regarding the changing epidemiology as well as the risk of transmission of HIV disease in the health care setting. Relative ignorance in these areas can lead to increased risk of nosocomial infection to both the doctor and the patient.

The number of reported acquired immunodeficiency syndrome cases continues to increase. Between December 1989 and November 1990, a total of 42,442 AIDS cases were reported to the Centers for Disease Control for the United States and its territories, which represented an annual rate of 16.7 cases per 100,000 population.<sup>1</sup> Figures for the same period between 1988

and 1989 were 35,614 and 14.1, respectively.<sup>1</sup> The 1989 figures represent a 9% increase over the 1988 rates.<sup>2</sup> The cumulative total of AIDS cases reported through November 1990 was 157,525,<sup>1</sup> which indicates the explosive nature of the epidemic.

Although the number of AIDS cases is known with reasonable accuracy, the seroprevalence of HIV is much more difficult to assess.<sup>3</sup> In 1988 the estimated number of seropositive individuals ranged from 400,000 to 2 million.<sup>3</sup> A study conducted in sexually transmitted disease clinics in New Mexico found an overall male seropositive rate of 2.4%, whereas the rate in homosexual/bisexual males was 14.3%.<sup>4</sup> The homosexual/bisexual group continues to have the highest rate of infection with reported sero-



prevalences ranging from 10% to 70%<sup>5</sup> and accounting for more than 50% of reported AIDS cases.<sup>1,2</sup> Intravenous drug users also continue to be a high-risk group, constituting 23% of the reported AIDS cases.<sup>2</sup> The seroprevalence among intravenous drug users appears to be partially related to geographic and socioeconomic factors, because reported rates range from 50% to 60% in New York, New Jersey, and Puerto Rico to less than 5% in most other metropolitan and rural areas of the country.<sup>5</sup>

A third group at high risk are individuals with hemophilia. It is estimated that 70% of individuals with hemophilia A and 35% of individuals with hemophilia B are HIV seropositive,<sup>5</sup> but trends in actual AIDS cases suggest that rates of infection among both hemophiliacs and recipients of blood transfusions are stabilizing.<sup>2</sup> This stabilization appears to be the result of both improved donor screening and heat treatment of factor concentrates.

Information on the HIV status of the general population can be extrapolated, albeit with caution, from studies of selected population segments. Blood donors represent a population screened for known risk factors. Between 1985 and 1989, 0.043% of first-time blood donors were HIV seropositive.<sup>5</sup> Of those HIV-seropositive individuals who could be reached for interview, 80% to 90% were found to have risk factors for HIV infection. Similarly, Castro and associates<sup>6</sup> showed that 72% of patients originally described to have AIDS without identified risk factors did indeed have risk factors when follow-up information was obtained.

There has been increased scrutiny of prospective donors of corneas for transplantation. Seropositive rates reported among corneal donors in Houston<sup>7</sup> and Michigan<sup>8</sup> were 0.33% and 0.84%, respectively. Conway and Insler<sup>9</sup> reported the results of HIV testing of 8,787 corneal donors, which represented 26% of the total potential corneal donors in North America during 1986. They found an HIV seroprevalence of 0.68%.

With the exception of intravenous drug users, HIV disease is notably more common in males than females. The cumulative total of reported AIDS cases, including pediatric cases, through November 1990 for males was 141,131 compared with 16,394 for females.<sup>1</sup> The ratio of HIV-infected male-to-female adults is approximately 13 to 1, whereas for heterosexual adult patients with AIDS the ratio is 2.9 to 1.<sup>5</sup> Male-to-female ratios for blood donors and military applicants were 4.6 to 1 and 5.5 to 1, respectively.

ly.<sup>5</sup> Blacks and Hispanics have 3.0 and 2.6 times greater incidences of AIDS compared to whites. These ratios increase to 12.0 and 9.3, respectively, when homosexual and bisexual men are excluded,<sup>5</sup> which suggests that these groups are more likely to acquire HIV by intravenous drug use or heterosexual transmission.

Although this information is consistent with many of our preconceived notions about HIV and AIDS, the epidemiology of this disease is changing. Individuals older than the age of 50 years are making up a larger percentage of AIDS cases. In 1981, patients older than 50 years made up 6.9% of the reported AIDS cases. This increased to 10.9% by 1987 and has remained approximately 10% since that time.<sup>10</sup> Evidence also suggests that the HIV epidemic is disproportionately increasing in geographic areas of traditionally low incidence, such as rural America.<sup>4,11</sup>

As the epidemic of HIV grows so does the number of heterosexually acquired cases, but the proportion of heterosexually acquired AIDS cases has remained stable at approximately 5% from 1983 to 1988.<sup>12</sup> Both male-to-female and female-to-male transmission has been reported,<sup>13</sup> with transmission rates ranging from 8% to more than 50%.<sup>14-16</sup> Data have been conflicting when correlating the number of contacts by an infected patient and the probability of seroconversion. Transmission of HIV has been reported after only one heterosexual contact between a woman and her infected partner,<sup>14,15</sup> whereas some women have reported more than 200 contacts without HIV transmission.<sup>14</sup> It has also been suggested that male-to-female transmission may be more efficient than female-to-male transmission.<sup>14</sup>

The incubation period, or latency period, from HIV infection to AIDS is often difficult to assess because of the frequently unknown date of infection. Blood transfusion-acquired AIDS cases are unique in that the date of exposure is usually known with relative accuracy. A retrospective study of 1,206 transfusion-associated AIDS cases for which the date of transfusion was known showed that only 8% of those patients developed AIDS within three years.<sup>17</sup> The same study suggested that of those patients who develop AIDS within eight years of transfusion approximately 75% do so after 5.2 years and 50% after 6.7 years. A more recent study suggested that the incubation period of AIDS may be lengthening.<sup>18</sup> The impact of this long incubation period on assessing the magnitude of the epidemic is obvious.

The potential impact of seronegative HIV infection is not yet known.<sup>19-21</sup> Imagawa and associates<sup>20</sup> reported the detection of HIV-1 by culture and DNA amplification in 31 of 133 seronegative homosexual men (23%) in Los Angeles. The study population was selected because of their continued involvement in high-risk activities. In 27 of these individuals seroconversion was not demonstrated until 28 to 36 months after viral isolation. Serologic reversion has also been demonstrated.<sup>21</sup> Although the incidence of seroreversion appears to be low (0.4%), patients have been reported to become seronegative by both enzyme-linked immunosorbent assay and Western blot analysis while still containing HIV-1 DNA within their peripheral blood mononuclear cells.<sup>21</sup> Three serologic patterns of HIV infection have been proposed<sup>22</sup>: (1) antibody levels increase to high levels within the first six weeks of infection and remain increased throughout the course of the disease; (2) patients serologically revert to an HIV-negative state by enzyme-linked immunosorbent assay and Western blot analysis after a prolonged seropositive period; and (3) patients seroconvert only after a prolonged period of infection. The question of whether seronegative individuals can transmit HIV infection to others remains unanswered.

Health care workers are often exposed to patients' bodily fluids and thus are at risk of contracting blood-borne diseases.<sup>23-27</sup> Although studies on ophthalmologists and ophthalmic procedures have not been conducted, several reports of HIV seroconversion in individuals providing health care have been published.<sup>28-32</sup> In a 1984 report, a nurse who had a needle-stick injury to her finger with the possible injection of a small quantity of blood seroconverted in seven weeks.<sup>28</sup> Human immunodeficiency virus seroconversion has also been demonstrated in a health care worker who received a deep intramuscular needle stick with a large-bore needle.<sup>29</sup> These two cases each had a significant inoculum, but seroconversion has also been reported after a superficial needle stick.<sup>30</sup> Three of these individuals<sup>28,29,31</sup> had postneedle-stick viral (influenzalike) illnesses consisting of fever, myalgias, sore throat, and in two cases<sup>28,31</sup> a macular rash. These episodes occurred two weeks to two months after needle-stick exposure. In 1986, the Centers for Disease Control reported the transmission of HIV infection, with seroconversion, from a 24-month-old HIV-infected child to his mother who was providing intensive at-home health care.<sup>32</sup> The

mother could not recall an episode of potential parenteral exposure while providing care but did recall several instances of skin exposure to contaminated bodily fluids.

These cases demonstrate that HIV-positive patients can transmit infection to health care workers. Identifying the HIV-positive individual in the health care setting, however, is often difficult. The HIV seroprevalence in emergency room patients has been shown to be as high as 5.2%,<sup>33</sup> with the rate among those patients with unknown HIV status being 4.0%. Ophthalmologists are often involved in the examination and care of trauma patients. Patients who had penetrating trauma were significantly more likely to be HIV seropositive than other emergency room patients,<sup>33,34</sup> with an incidence of HIV seropositivity as high as 19%.<sup>34</sup> Two of five patients who had HIV risk factors and claimed to be HIV seronegative were HIV positive when tested in the emergency room.<sup>33</sup> Thus, it appears that the history of a previous HIV-negative status in a patient with known risk factors for HIV may not be reliable. Both of these studies were conducted at inner-city trauma centers.

Early studies of the nosocomial risk of HIV infection failed to disclose seroconversion in exposed health care workers.<sup>35-38</sup> In 1988, the Centers for Disease Control<sup>39</sup> reported that the epidemiology of AIDS among health care workers was not significantly different from that for the general population. The same report, however, claimed that the risk of seroconversion after parenteral exposure to HIV-positive material was approximately 0.5% and that seroconversion seemed to take place within six months of exposure. Seroconversion rates of up to 0.94% have been reported for health care workers parenterally exposed to HIV-contaminated blood.<sup>40,41</sup> A more recent study found that only one of 159 (0.56%) health care workers who reported a percutaneous HIV exposure seroconverted.<sup>42</sup> This health care worker had a deep cut from a contaminated sharp object. The rate of seroconversion appears to be similar for laboratory workers working with concentrated HIV.<sup>43</sup>

The Centers for Disease Control have issued guidelines, which are periodically updated, for the prevention of transmission of HIV as well as other blood-borne pathogens. The Centers for Disease Control currently recommend the use of universal precautions for the handling of blood and certain bodily fluids,<sup>41,44,45</sup> regardless of the presence of HIV infection with the as-



sumption that all patients are capable of transmitting HIV and other blood-borne diseases. Barriers to skin and mucous membrane contamination should be used when handling potentially contaminated fluids. These barriers include gloves, gowns, aprons, masks, and protective eye wear when appropriate. Contaminated skin should be washed immediately, as should hands after removal of gloves. Special care should be taken to prevent injuries from sharp instruments. Needles should not be re-capped, bent, broken, or manipulated by hand. Puncture-resistant containers should be located conveniently for the disposal of all sharp instruments. Mouthpieces or other ventilation devices should be available when their need is predictable. Bodily fluids that the Centers for Disease Control considers potentially infectious include blood, any fluid containing visible blood, semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid.<sup>45</sup> Feces, nasal secretions, sputum, sweat, saliva, tears, urine, and vomitus are excluded unless they contain blood.<sup>45</sup>

Despite these recommendations, the adherence to universal precautions is generally poor. The Cooperative Needlestick Surveillance Group reported that up to 40% of reported HIV exposures could have been prevented if recommended precautions were observed.<sup>40</sup> Needles are a potential source of infection in ophthalmic practice. Common outpatient procedures during which this kind of exposure can occur include local anesthetic blocks, anterior chamber paracentesis, and postvitrectomy gas-fluid exchanges. Gerberding and associates<sup>37</sup> reported a 56% inadequate precaution rate among health care workers dealing with known patients with AIDS and HIV-positive material. A more recent study showed that universal precautions adherence among house staff was only 16% but could be increased to 62% by providing them with universal precaution packs containing the necessary equipment.<sup>46</sup> Preventive compliance is therefore enhanced by continuing reminders of HIV exposure.

Surgery in patients with HIV infection confronts the surgeon with sometimes difficult choices. Some might argue that surgical intervention in patients with HIV disease might put these patients at increased risk of infection and morbidity. Although surgery and anesthesia are known to cause immunodepression, there is no evidence that suggests that this markedly accelerates HIV disease.<sup>47</sup> The risk-benefit ratio

of a procedure must be carefully examined when dealing with patients with AIDS. Less invasive procedures with lower morbidity can be substituted, in some cases, for elective surgical procedures. The patient's life expectancy must also be considered when planning for visual rehabilitation. Small-incision cataract extraction may be preferable to traditional extracapsular extraction. Similarly, silicone oil retinal tamponade may be superior to gas tamponade in HIV-associated retinal detachments because of the faster rehabilitation time and lack of need for prolonged positioning.

It has been suggested that physicians have an obligation to treat patients with AIDS but that this obligation can be limited under certain rare circumstances.<sup>48</sup> Although some physicians argue that the risk of nosocomial HIV infection overrides their obligation to the patient, physicians have long known that they are at increased risk of potentially fatal diseases such as hepatitis B.<sup>23,24</sup> By becoming physicians we have accepted the risks that we know to be part of the profession and thus cannot forgo our responsibilities. An exception to this responsibility may be the pregnant physician, where the rights of the unborn child can be considered. Excessive risk to any one physician can be limited by having all physicians assume their professional obligations to these patients.

The actual risk of HIV infection for a surgeon depends on several factors, including the prevalence of HIV in the population being treated, the frequency and nature of exposures, and the effectiveness of precautions. Both vinyl and latex gloves have been shown to be effective barriers to virus particles,<sup>49</sup> but glove perforation rates during general surgery have been reported to be as high as 48.2%.<sup>50</sup> A survey of surgeons in the New York City area reported that 86% of the surgeons responding had had a puncture injury during the previous year and that 67% of these injuries occurred in the operating room.<sup>51</sup> Other studies reported injury and exposure rates of 5.6% and 6.4%, respectively, per operation.<sup>52,53</sup> One of these studies suggested that general surgeons were at higher risk than other specialties.<sup>52</sup> A report from San Francisco General Hospital suggested that trauma surgery, plastic surgery, obstetric and gynecologic surgery, and orthopedic surgery carry the highest risk of intraoperative exposure.<sup>53</sup> A statistically significant association was found between exposure and intraoperative blood loss of greater than 300 ml or operative time of greater than three hours. Preoperative HIV test-

ing is generally believed to be unnecessary when universal precautions are properly observed.<sup>54</sup> The knowledge of a patient's HIV risk factors has been shown not to make a difference in surgeons' intraoperative exposure rate.<sup>53</sup>

Ophthalmology differs from other surgical specialties in that exposure to blood is often limited; however, HIV has been isolated from several ocular tissues, including retina, iris, conjunctiva, and cornea.<sup>55</sup> Human immunodeficiency virus antigen has also been detected in the vitreous of patients with AIDS both with and without cytomegalovirus retinitis.<sup>56</sup> Studies of the tears of patients with AIDS have disclosed HIV,<sup>57</sup> as have studies on contact lens rinsing solutions and high-water soft contact lenses worn overnight.<sup>58</sup> Given the limited blood and contaminated fluid exposure during ophthalmic surgery, universal precautions should ensure a reasonable degree of safety from HIV infection. Although in some institutions the practice of double gloving is routine,<sup>53</sup> this is of uncertain value in ophthalmic surgery.

Office ophthalmic practice presents different problems. Tears and ocular surface tissues have been demonstrated to potentially harbor HIV; therefore, special precautions should be taken to prevent the spread of infection from these tissues. The Centers for Disease Control in 1985 recommended that after coming in contact with tears, health care workers should wash their hands, and gloves should be worn if any open wounds or dermatologic conditions exist on the hands.<sup>59</sup> Others recommended that gloves should be worn when the patient is a known HIV carrier.<sup>60</sup>

Instruments coming in contact with the ocular surface or tears should be wiped clean and then disinfected by one of the following procedures: five- to ten-minute exposure to 3% hydrogen peroxide; a fresh solution of 5,000 parts per million of free chlorine (1:10 dilution of common household bleach); 70% ethanol; or 70% isopropanol. Contact lenses used in trial fittings should be disinfected by either a heat disinfection or hydrogen peroxide system, depending on the type of contact lens.<sup>59</sup> A study from the Helsinki University Eye Hospital,<sup>60</sup> however, was unable to isolate HIV from the tonometer prism after applanation in three HIV-positive patients.

The hazard of acquiring HIV in the health care setting may not only be to the health care worker but also to the patient. Most recently the Centers for Disease Control reported a series of cases of HIV transmission from a dentist to

three of his patients.<sup>61,62</sup> Sequencing of HIV-proviral DNA disclosed a degree of relatedness between the patients' HIV and the dentist's that statistically was much greater than would be expected by chance alone ( $P = .006$ ).<sup>62</sup> All three patients had undergone invasive dental procedures by the dentist while he was infected with HIV. The patients had no risk factors for infection, and no other dental office personnel were HIV positive. The Centers for Disease Control therefore recommended the use of universal precautions to help prevent the transmission of blood-borne pathogens to both health care workers and their patients.

Exact policies regarding postexposure treatment of health care workers may vary, but recommendations have been issued.<sup>63,64</sup> After a percutaneous or mucous membrane exposure to a bodily fluid for which universal precautions should be maintained, it is recommended that details of the exposure be recorded, and if possible the source patient should be tested for HIV. If the source patient is HIV negative no further follow-up for HIV is needed. If the source patient is HIV positive or refuses testing, the exposed worker should be tested as soon as possible for HIV. If the initial HIV testing is negative the worker should be retested periodically for at least six months. The use of zidovudine in the prophylaxis of postexposure HIV infection is controversial and not considered necessary by the Centers for Disease Control.<sup>64</sup> Some health care institutions, however, do offer zidovudine to their exposed workers.

Human immunodeficiency virus infection is no longer a disease of selected subgroups of the population. The disease is now appearing in individuals of traditionally low risk, but the calculation of prevalence is complicated by a long incubation period and an unknown contribution from seronegative disease. Health care workers are at risk, although limited, for nosocomial infection, with the seroconversion rate after a parenteral exposure to HIV being less than 1%.<sup>39,41,42</sup> Ophthalmologists are at lower risk than other surgical specialties because of the limited blood exposure during common ophthalmic procedures. Nevertheless, universal precautions, particularly concerning needles, should be observed. As many as two thirds of needle-stick injuries take place during the process of needle disposal.<sup>65</sup> Clearly, institutions should have guidelines for infection control, which include employee education, and supply personnel with adequate resources to implement universal precautions effectively.<sup>46</sup>



Although some physicians may believe that they are at excessive risk of acquiring HIV during the practice of medicine, this is not the case for ophthalmologists. Thus, ophthalmologists cannot divorce themselves from the necessity to treat these patients. To the practicing ophthalmologist HIV disease and AIDS may be infrequently encountered, but as these patients survive for longer periods of time<sup>66</sup> the ophthalmologist will be called upon more often to examine and treat these patients.<sup>67,68</sup> As medical science continues to learn about HIV more ophthalmic manifestations will undoubtedly be uncovered, which will necessitate more ophthalmologic care in the management of HIV disease.

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## LETTERS TO THE JOURNAL

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### Development of Scleral Ulceration and Calcification After Pterygium Excision and Mitomycin Therapy

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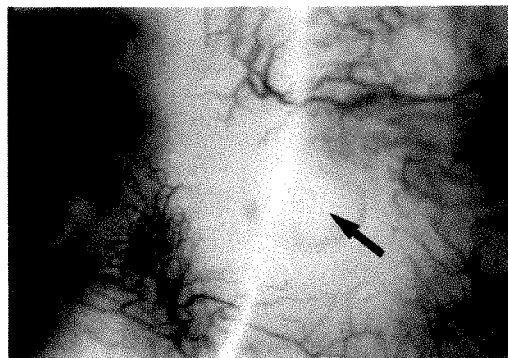
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Various medical treatments are used to prevent recurrence of pterygia after excision. These treatments include cautery, beta irradiation, topical corticosteroids, and thiotepe (triethylene thiophosphoramide).<sup>1</sup> Mitomycin, an antineoplastic-antibiotic agent, has been reported to be a safe and effective adjunct to surgical excision.<sup>2,3</sup> At concentrations of 0.04% or less, mitomycin is well tolerated. Reported side effects include conjunctival irritation, tearing, and superficial keratitis; scleral ulceration is infrequent. We recently saw a patient who developed scleral calcification after pterygium excision and topical treatment with mitomycin.

A healthy, 37-year-old white woman underwent primary excision of a pterygium of her right eye by means of a bare sclera technique. Postoperatively she used mitomycin 0.04% and topical corticosteroids four times daily for two

weeks without incident. Eleven months later, she developed irritation and redness in the right eye. Examination disclosed a  $2.5 \times 4.0$ -mm conjunctival epithelial erosion that surrounded a partial-thickness scleral defect at the site of the previous pterygium operation. The superior aspect of the defect was calcified. She was treated with topical neomycin-polymixin B-dexamethasone and ocular lubricants with patching, but the erosion did not heal over the next two months, and she was referred to the Proctor Foundation.

Her uncorrected visual acuity was 20/20 in each eye. The left eye was unremarkable except for a pinguecula. The right eye had a  $2 \times 1$ -mm white plaque at the 3 o'clock position, which filled a partial-thickness scleral ulceration with an overlying epithelial defect (Figure). The



**Figure** (Dunn and associates). Calcific plaque at site of pterygium operation (arrow).

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Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

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plaque was gritty and firmly adherent to the underlying sclera. The adjacent conjunctiva was slightly raised and injected. The cornea was clear. Results of the remainder of the ocular examination were normal.

The plaque was removed under local anesthesia. The underlying sclera was intact and the area healed uneventfully. Histopathologically the plaque stained with Alizarin red, suggesting that it was calcific.

Mitomycin inhibits the synthesis of DNA, RNA, and protein. Several studies have demonstrated that topical mitomycin reduces recurrence rates after pterygium excision.<sup>2,3</sup> Complications include pain, photophobia, lacrimation, foreign-body sensation, and noninfectious scleral ulceration. Regimens of mitomycin 0.02%, twice daily for five days,<sup>3</sup> or 0.04% four times daily for two weeks,<sup>2</sup> have been reported to reduce recurrence rates with only mild and temporary side effects.

Scleral calcification attributable to mitomycin has been previously described in the Japanese literature.<sup>4</sup> Intramural bladder calcification was reported after bladder irrigation with mitomycin for treatment of superficial bladder cancer.<sup>5</sup> Although the pathogenesis of calcification is not known, it may represent an extreme form of mitomycin-induced degenerative changes in the tissue.

We report this case to alert ophthalmologists to another potential complication of topical mitomycin therapy after pterygium excision.

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## Parinaud's Oculoglandular Syndrome Simulating Lymphoma

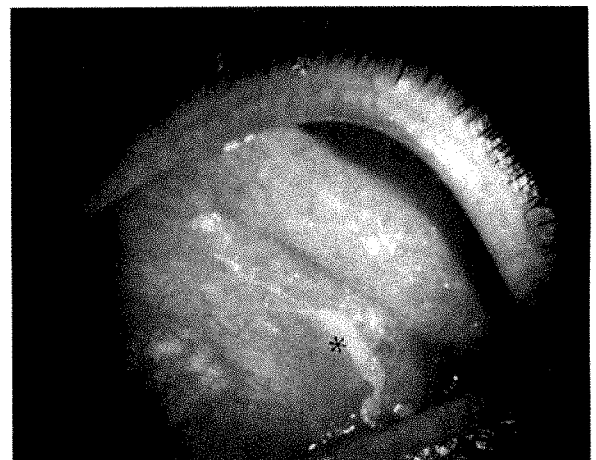
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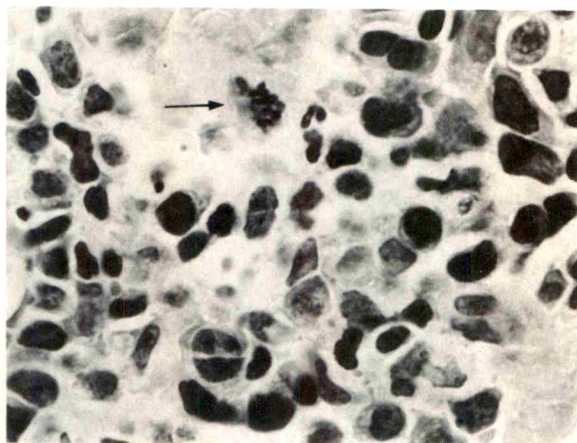
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Parinaud's oculoglandular syndrome refers to a type of unilateral conjunctivitis associated with ipsilateral regional lymphadenitis and, occasionally, constitutional symptoms. A variety of infectious agents can cause the syndrome, but the cat-scratch bacillus is probably the most common cause.<sup>1</sup> The type of inflammation may vary from predominately granulomatous to suppurative.<sup>2</sup> We treated a patient with Parinaud's oculoglandular conjunctivitis that histologically simulated a malignant lymphoma.

A 49-year-old man had a three-day history of swollen left eyelids, a red eye, and tenderness and swelling anterior to the left ear. He had been bitten on the upper lip by the family kitten four weeks previously. Minor bleeding occurred at the site of injury and in a few days a pustule had formed. On examination, the left eye had a mucopurulent discharge. The bulbar and tarsal conjunctivae were markedly injected and demonstrated follicles on the lower palpebral conjunctiva and a diffuse papillary reac-



**Fig. 1** (Fanous and Margo). An erythematous nodule (asterisk) is present in the superior bulbar conjunctiva separate from the palpebral lobe of the lacrimal gland. The conjunctiva is diffusely injected and has a mucopurulent discharge.



**Fig. 2** (Fanous and Margo). The conjunctival biopsy specimen shows large atypical lymphocytes with dense nuclear chromatin and variable nuclear shapes. A mitotic figure (arrow) is present (hematoxylin-eosin,  $\times 450$ )

tion. A 3-mm erythematous nodule was present in the superotemporal bulbar conjunctiva separate from the palpebral lobe of the lacrimal gland (Fig. 1). An ipsilateral preauricular node was enlarged and tender. Half of a biopsy specimen of the conjunctival mass was sent for bacterial and fungal cultures. Tetracycline, 500 mg taken orally three times a day, and topical sulfacetamide 10% to the left eye four times a day were prescribed.

Pertinent laboratory studies disclosed a normal complete blood cell count; serologic tests for syphilis were negative (hemagglutination treponemal test for syphilis and rapid plasma reagin). An IgG titer to Epstein-Barr viral capsid antigen was positive but the IgM titer was negative. A purified protein derivative skin test was negative. Bacterial and fungal cultures were negative.

The conjunctival biopsy specimen consisted of a diffuse proliferation of large mononuclear cells, many of which showed considerable nuclear hyperchromatism and atypia (Fig. 2). Scattered nuclear debris, plasma cells, and a few eosinophils were present but only at the periphery of the specimen; granulomas were not seen. Special stains for fungi and acid-fast bacteria were negative as was the Warthin-Starry stain for the cat-scratch bacillus. The diagnosis of the biopsy specimen was described as atypical lymphoid hyperplasia and the slides were referred to the hematopathology laboratory for review. The specimen was interpreted by two pathologists as a large-cell lymphoma.

They requested additional fresh tissue for immunofluorescence studies and flow cytometry, and further histologic sections.

When the patient returned three weeks later for a second biopsy and lymph node aspirate after completing his course of tetracycline, the examination results were normal. The conjunctiva was clear and the regional adenopathy resolved. The Hanger-Rose intradermal skin test for cat-scratch disease was positive (1.3 cm induration) at 48 hours.

Several benign conditions histologically simulate malignant lymphoma.<sup>3</sup> We are aware of at least one case of cat-scratch disease in which a biopsy specimen of the preauricular mass was mistaken histologically for a lymphoma.<sup>4</sup> The distinction between lymphoma and reactive lymphoid hyperplasia can be difficult, particularly when the size of the specimen is small.

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## Ocular Sarcoidosis Manifesting as an Anterior Staphyloma

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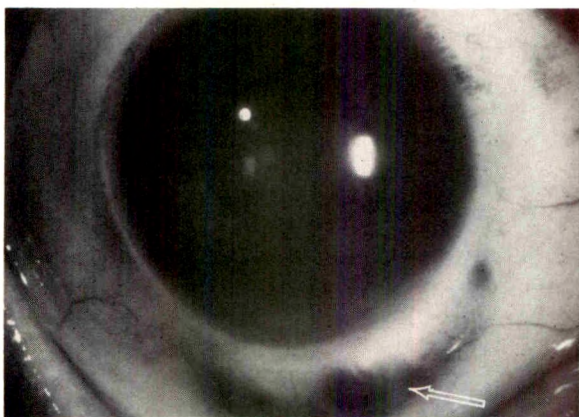
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Sarcoidosis is a multisystem granulomatous disease of unknown cause. It frequently affects



the lungs, skin, and eyes.<sup>1,2</sup> Ocular sarcoidosis manifests itself in a variety of ways including conjunctival granulomas, keratoconjunctivitis sicca from granulomatous infiltration of the lacrimal gland, anterior, intermediate, and posterior uveitis, retinal vasculitis, and optic nerve involvement with disk edema, optic neuritis, or optic atrophy.<sup>1,2</sup>

A 38-year-old black woman complained of ocular pain and blurred vision in her right eye, which had begun one week previously. She had had several episodes of ocular discomfort and blurred vision in the same eye over the previous 12 months. Systemic sarcoidosis had been diagnosed two years previously when the patient was found to have hilar lymphadenopathy and interstitial lung disease, as well as recurrent calcium oxalate kidney stones secondary to hypercalcemia. The patient had not previously visited an ophthalmologist concerning her symptoms. She denied any use of systemic, periocular, or topical corticosteroids. Her visual acuity without correction was R.E.: counting fingers at 6 inches and L.E.: 20/30. Slit-lamp examination of the right eye disclosed a 9 × 1.5-mm inferior circumlimbal staphyloma completely covered by conjunctiva (Figure). The area overlying the staphyloma was elevated 1 to 2 mm and appeared taut. Further examination of the anterior segment showed diffuse microcystic edema of the cornea with mutton-fat and pigment keratic precipitates on the endothelium, moderate cell and flare in the anterior chamber, and focal areas of posterior synechiae. The left eye was unremarkable. Intraocular pressure by applanation tonometry was 26 mm Hg in the right eye and 16 mm Hg in the left



**Figure** (Zeiter and associates). Right eye with posterior synechiae and perilimbal anterior staphyloma

eye. There was a red reflex without retinal detail in the right eye and the fundus of the left eye was normal. The patient was treated with orally administered prednisone (80 mg/day), topical 1% prednisolone acetate, 0.5% timolol maleate, and 5% homatropine.

When the patient returned one week later there was marked symptomatic improvement. Uncorrected visual acuity was R.E.: 20/200 and L.E.: 20/30. The inferior perilimbal staphyloma was still present, but the microcystic edema of the cornea had cleared and the number of keratic precipitates had markedly decreased. Intraocular pressure by applanation tonometry was 26 mm Hg in the right eye and 12 mm Hg in the left eye. Gonioscopy of the right eye disclosed 360 degrees of peripheral anterior synechiae. Fundus examination disclosed a cup/disk ratio of 0.9 in the right eye and 0.4 in the left eye. The patient could not be given carbonic anhydrase inhibitors because of her kidney problems, and three days later she underwent an uncomplicated trabeculectomy in the right eye. Two weeks later, the patient was asymptomatic with a best-corrected visual acuity of R.E.: 20/100 and L.E.: 20/20. Slit-lamp examination of the right eye showed a functioning fistula superiorly with a diffuse conjunctival bleb. The inferior perilimbal staphyloma had decreased in height and area. The anterior chamber was deep and quiet. Applanation tonometry disclosed intraocular pressures of 12 mm Hg in the right eye and 16 mm Hg in the left eye with no medications. With the reduction of intraocular pressure and control of inflammation, we elected to observe the staphyloma closely. After eight months there was no change in the size of the staphyloma, and the intraocular pressure of the right eye remained between 12 and 15 mm Hg.

Staphyloma formation results from the interaction of the distending force provided by the intraocular pressure and the tensile strength of the sclera. In a normotensive eye, staphylomas occur where scleral tensile strength is reduced.<sup>3</sup> This reduction in scleral tensile strength may be secondary to noninflammatory thinning disorders such as axial myopia or congenital colobomas.<sup>3</sup> Loss of tensile strength may also result in areas of traumatic scleral dehiscence as well as areas of scleral destruction by episodes of vasculitis associated with collagen vascular diseases or chronic uveitis.<sup>3</sup> In eyes with increased intraocular pressure the distending effects may exceed the normal scleral tensile strength to create a staphyloma. The sclera between the

ciliary body and the corneoscleral limbus is one such area where distending pressure may exceed scleral tensile strength, thus resulting in a staphyloma. This is exemplified by our patient who had severe uveitis and secondary glaucoma, both of which resulted from sarcoidosis.

By LaPlace's Law, once a staphylomatous area begins to protrude, the tension in the sclera over that area is greater than in adjacent, noninvolved sclera. This increased tension results in progressive ectasia. To arrest growth of the staphyloma, one must either restore tensile strength or lower the distending pressure. In our patient, intraocular pressure was successfully reduced with a trabeculectomy, thereby reducing the scleral tension over the staphyloma. This reduction in scleral tension resulted in a marked decrease in the amount of protrusion of the staphyloma, thus averting the need for a scleral-patch grafting procedure.

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### Spontaneous Reattachment of a Total Retinal Detachment in an Infant with Microphthalmos and an Optic Nerve Coloboma

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Colobomas and optic nerve pits are closely related and are the result of incomplete closure of fetal tissue.<sup>1</sup> They often occur with sensory macular retinal detachments, and visual symptoms and are usually found in persons over 20 years of age. A variety of methods have been advocated for treating the associated sensory retinal detachments. These treatments include patching, bedrest, corticosteroids, vitrectomy, scleral buckling procedures, gas-fluid exchange, and photocoagulation.<sup>2</sup> Spontaneous reattachment has also been reported.<sup>1,3,4</sup> We encountered a total retinal detachment with subsequent spontaneous reattachment in an infant with a microphthalmic eye and an optic nerve coloboma.

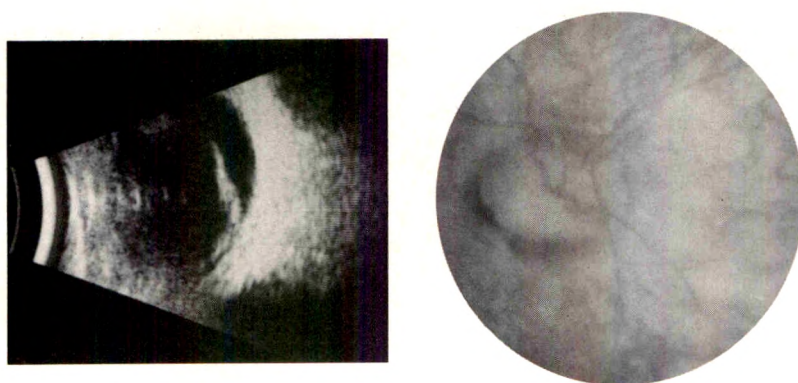
At pediatric examination, a neonate had a small left eye. When the infant was 2 weeks of age, ophthalmic examination disclosed relative enophthalmos in the left eye and light perception in both eyes with no afferent pupillary defect. The corneas were clear and measured 11 × 11 mm in the right eye and 9.5 × 10 mm in the left eye. Ophthalmoscopy disclosed a normal right eye; however, a temporal retinal detachment involving the macula was present in the left eye. The retinal detachment was confirmed by ultrasound (Figure, left).

Examination of the infant under anesthesia at 7 weeks of age disclosed a completely detached retina and a colobomatous optic nerve with an inferior shallow optic nerve pit. A fine, white stalk thought to represent persistent hyaloid tissue extended close to the back of the lens. Ultrasound showed a funnel-shaped total retinal detachment. The space outside the funnel was filled only with fluid. Intraocular pressure was 5 mm Hg in the right eye and 15 mm Hg in the left eye. Magnetic resonance imaging disclosed no intracranial abnormalities.

The infant was reexamined under anesthesia at 6 months of age, and the retina had completely reattached (Figure, right). Pigmentary stippling of the macular area with a decreased foveal reflex was present as well as peripheral atrophic spots and pigmentary changes consistent with a previous retinal detachment.

The cause of retinal detachments associated with optic nerve colobomas and pits is unknown. Theories previously reported include communication of the subretinal space with cerebral spinal fluid, communication with the vitreous, or leakage of the peripapillary circulation.<sup>2,3</sup> In adults a three-month period of observation has been recommended before laser treatment, gas injection, vitrectomy, or air-fluid





**Figure** (Bochow and associates). Left, Ultrasound B-scan demonstrates retinal detachment. Right, Optic nerve coloboma and reattached retina.

exchange,<sup>2</sup> but the treatment of infants is less clear. One should keep in mind the possibility of spontaneous reattachment of retinal detachments in patients with optic nerve pits and colobomas.

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by shoulder-girdle weakness. Sporadic, autosomal-dominant, and x-linked recessive cases have been reported.<sup>2</sup> There are no known ocular associations with scapuloparoneal muscular dystrophy. We encountered a case of scapuloparoneal dystrophy with retinal telangiectasis.

A 25-year-old woman complained of floaters in her left eye. Best-corrected visual acuity was R.E.: 20/25 and L.E.: 20/30. Ophthalmoscopic examination disclosed tortuosity and telangiectasis of the blood vessels in the far temporal periphery of each eye. Localized old vitreous hemorrhage was present inferotemporally in the right eye, and a recent vitreous hemorrhage was visible in the left eye. Results of the remainder of the ocular examination were normal. Fluorescein angiography showed telangiectatic vessels that leaked fluorescein in the periphery of each eye (Figure). Transconjunctival cryopexy was performed to close the abnormal vessels in the left eye.

A complete medical history disclosed that the patient had had some delay in walking second-

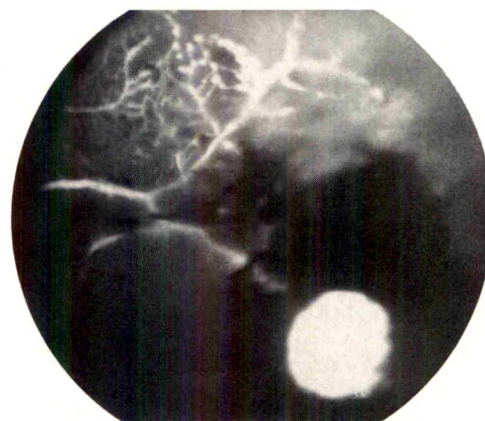
### Retinal Telangiectasis in Scapuloperoneal Muscular Dystrophy

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Scapuloparoneal muscular dystrophy is a rare myopathy of the proximal shoulder and anterior leg muscles.<sup>1</sup> Patients develop foot drop early in the course of the disease, followed



**Figure** (Daily and Dickey). Fluorescein angiogram of the left eye showing vascular telangiectasis with overlying vitreous hemorrhage.

dary to contracted achilles tendons, which were surgically corrected between the age of 3 and 4 years. Occasional shoulder achiness and weakness began when the patient was about 15 years old. Within the past year she had noticed some painless arm weakness when she opened jars or scooped ice cream. The patient had never noticed any facial weakness, difficulty in whistling, or difficulty sucking through a straw. Physical inspection of the patient disclosed posterior scapular winging on arm elevation, and small anterior leg compartments. A muscular dystrophy was suspected.

Neurologic consultation confirmed weakness in the scapuloparoneal distribution. Results were otherwise normal. Specifically, the facial muscles were uninvolved. Serum creatinine kinase and aldolase levels were normal. Results of nerve conduction velocity studies were normal, which excluded a neurogenic cause for the patient's weakness. Results of electromyography of several arm and leg muscles, and biopsy of the contralateral deltoid muscle were consistent with a myopathic process. Scapuloperoneal muscular dystrophy was diagnosed. The patient's father had Parkinson's disease. Her brother and sister had normal results from neuromuscular examinations. The mother was dead.

This case of retinal telangiectasis in scapuloperoneal dystrophy is unusual. Retinal telangiectasis has been reported in a similar muscular dystrophy, that of a facioscapulohumeral dystrophy, that of a facioscapulohumeral distribution.<sup>3,4</sup> Facioscapulohumeral dystrophy has prominent facial involvement and characteristically displays autosomal-dominant inheritance. The Research Group on Neuromuscular Diseases has classified scapuloperoneal dystrophy as a probable variant of facioscapulohumeral dystrophy, and this is a generally accepted position.<sup>5</sup> We recommend neurologic examination to exclude a muscular dystrophy in patients who have retinal telangiectasis not characteristic of Coats' disease.

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## Interferon Alpha 2a For Treatment of Age-Related Macular Degeneration

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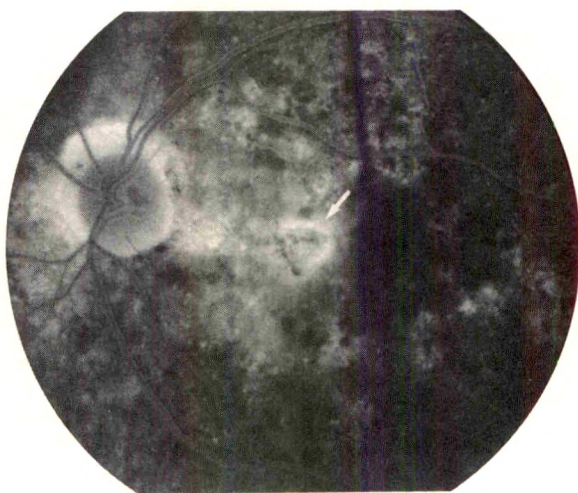
Recombinant interferon alpha 2a is a systemically administered drug that inhibits angiogenesis. It has been successfully used for the past 2½ years to treat rapidly progressive pulmonary hemangiomatosis and angiosarcomas in children.<sup>1</sup> In vitro, the drug inhibits endothelial cell migration<sup>2</sup> and shields receptor sites of endothelial cells from growth factors.<sup>3</sup>

Since January 1990, I have used this drug to treat seven patients with subretinal neovascular membranes secondary to age-related macular degeneration. The neovascular membranes were either completely within the foveal avascular zone or encroached onto this zone. Each patient signed an informed consent, and understood that other options consisted of laser photocoagulation or close observation.

In six eyes the membrane was 1 disk diameter or less in size. The initial visual acuity in the patients ranged between 20/40 and 20/100. The final visual acuity in five eyes was between 20/25 and 20/70. Each eye demonstrated a reduction in the size of the scotoma. One eye, considered a failure, improved from 5/200 to 20/60 after six weeks of treatment. After treatment with the drug for one month, a recurrence of the subretinal neovascular membrane resulted in a visual acuity of 20/100.

A membrane in the seventh patient was initially larger than 1 disk diameter. Visual acuity was 20/80. This membrane did not decrease in size as the other six smaller membranes did. The membrane became fibrotic, yielding final visual acuity of 5/200.





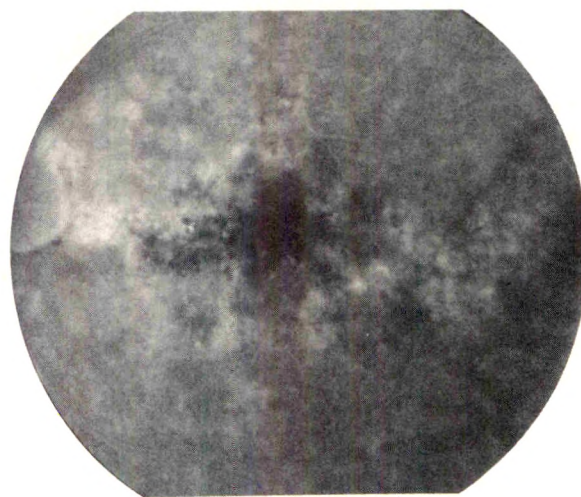
**Fig. 1** (Fung). Fundus of a 67-year-old woman, seen Sept. 11, 1990. Visual acuity was L.E.: 20/40 J10. Visual acuity in the right eye was finger counting at 1 ft secondary to a large disciform scar that had developed two years earlier. The arrow points to a subretinal neovascular membrane beneath the nasal macula. A thin layer of blood had already extended beneath the fovea.

Successful outcome was limited to recent, small, subretinal neovascular membranes.

Interferon alpha 2a was administered daily or every other day in small, subcutaneous injections. Each patient was examined by an oncologist/hematologist for baseline studies, and follow up examinations. To minimize the initial side effects, each patient received 1,500,000 units/m<sup>2</sup> of skin surface every other day for two doses. After that, they received 3,000,000 units/m<sup>2</sup> of skin surface every other day or Monday, Wednesday, and Friday of each week.

The dose is dependent upon the response of the abnormal subretinal membrane. The median total dose in these patients was  $75 \times 10^6$  units, given over a six- to eight-week period. The initial side effects were mild myalgia and fatigue. A low grade fever and anorexia were infrequent. Oral acetaminophen (Tylenol) minimized these symptoms. Complete blood cell counts were made every two weeks. No patient developed significant hematologic problems. The wholesale cost of  $75 \times 10^6$  units is approximately \$550.00. In this pilot study, the drug was provided by Roche Laboratories without charge.

Each patient had a complete ophthalmic examination with color and fluorescein photography (Figs. 1 and 2) every two weeks. In the successful cases, resolution of the membrane



**Fig. 2** (Fung). After seven weeks of interferon alpha 2a therapy (total dose of  $195 \times 10^6$  units) visual acuity was L.E.: 20/20 J1. To date, the patient's vision remains the same.

for four weeks was used as the end point to terminate the injections. In the unsuccessful case, treatment was stopped after  $90 \times 10^6$  units had been given with no evidence of a favorable response.

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## Spontaneous Filtration Blebs in a Patient With Microspherophakia

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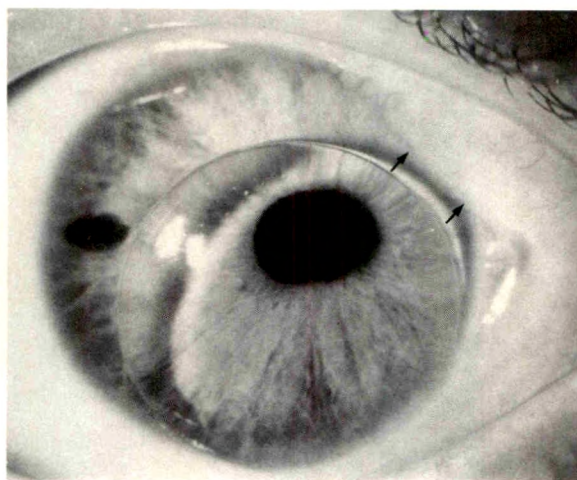
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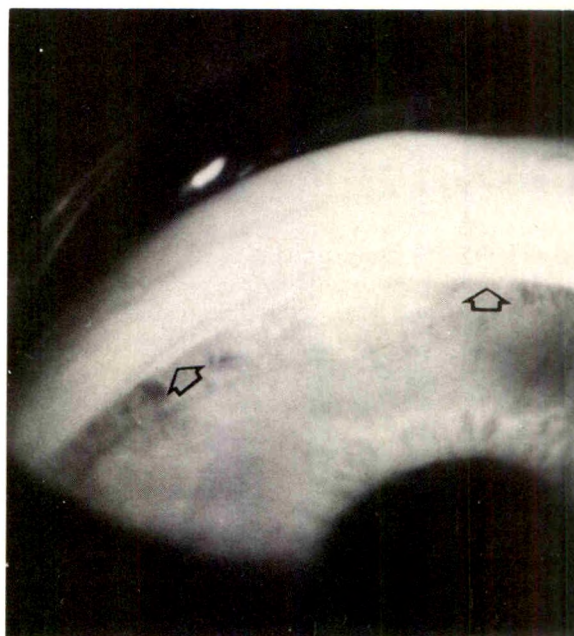


A 24-year-old white man with 20 diopters of myopia in each eye and normal intraocular pressures in both eyes had corneal edema in the right eye. There was no history of ocular trauma or family history of ocular disease. Pupillary dilation caused anterior subluxation of the patient's microspherophakic lenses. With the patient supine, the lenses were repositioned into the posterior chamber. The corneal edema in the right eye did not resolve and penetrating keratoplasty was performed. The operation was complicated by anterior subluxation of the lens with vitreous loss. This required an open-sky vitrectomy and wedge resection of the iris at the pupillary margin to maintain the lens in its normal anatomic position. A prophylactic laser iridotomy was performed in the left eye. Contact lenses were dispensed. Approximately four months later, bilateral nasal chemosis developed. The chemosis initially was attributed to contact-lens wear, but persistently low intraocular pressures and staphylomatous limbal changes prompted further examination.

At examination visual acuity was R.E.: 20/60 and L.E.: 20/40. Slight obliquity of the palpebral fissures, malar hypoplasia, frontal bossing, and septal deviation were present. The pupils were horizontally oval and decentered nasally. Slit-lamp biomicroscopy showed elevated, avascular, and microcystic nasal filtration blebs in both eyes (Fig. 1). No inflammation or peripheral corneal thinning was noted in either



**Fig. 1** (Pasquale and associates). Slit-lamp photograph of the left eye. Contact-lens wear was required to correct severe lenticular myopia. Staphylomatous limbal changes and a filtration bleb are present nasally. The cystic conjunctiva overhangs the peripheral cornea, superonasally (arrows).



**Fig. 2** (Pasquale and associates). Goniophotograph of the nasal angle of the left eye shows absence of limbal structures and a focal iris depression leading to a filtration cleft. Peripheral anterior synechiae (arrows) are present on either side of the filtration cleft.

eye. No iris transillumination defects were present except in an area of prior surgical manipulation in the right eye. Iridophacodonesis and microspherophakia were present bilaterally. However, the lenses were clear and well centered in the posterior chamber. Gonioscopy disclosed cavernous clefts in the areas of the filtration blebs (Fig. 2). Elsewhere, numerous peripheral anterior synechiae were scattered between areas of widely open angle. Intraocular pressure was 8 mm Hg in the right eye and 6 mm Hg in the left eye. The right optic disk had an ill-defined cup with mild posterior bowing of the temporal rim. The left disk was normal. There was neither posterior staphyloma nor choroidal effusion. The axial length measured 22 mm in each eye. Physical examination disclosed no arachnodactyly, brachymorphia-brachydactyly, joint or skin hyperextensibility, rash, or heart murmurs. A radiologic survey failed to disclose other skeletal abnormalities. Results of echocardiogram and electrocardiogram were normal.

Two other reported cases of filtration blebs without limbal surgery occurred after spontaneous rupture of Descemet's membrane in Terrien's marginal degeneration.<sup>1</sup> Although equatorial and limbal staphyloma can occur with



chronic glaucoma, the reason for limbal scleral dissolution and subconjunctival filtration in this case is unclear. Ectopia pupillae in our case was probably secondary to the pattern of peripheral anterior synechiae rather than an intrinsic iris abnormality. There was no evidence for a connective tissue disorder such as Marfan syndrome, Weill-Marchesani syndrome or Ehlers-Danlos syndrome. Despite slightly dysmorphic features, our patient's microspherophakia appears to be an isolated defect. Cases of mandibulofacial dysostosis (Treacher-Collins syndrome) with microspherophakia exist,<sup>2,3</sup> but salient features of this craniofacial deformity,<sup>4</sup> were absent in our case.

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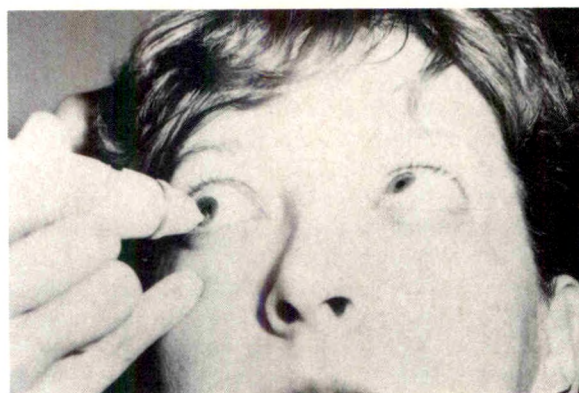
## Differential Intraocular Pressure in Restrictive Strabismus

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The possibility of a restrictive vs a paretic component has to be considered during the evaluation of an incomitant strabismus with limited ductions. This differentiation is important for diagnosis and surgical management, which in many cases will involve an attempt to release any significant restrictions. Ideally, the forced duction test is used to determine if a



**Fig. 1** (Muñoz and Capó). Patient with thyroid ophthalmopathy and a right hypotropia. In primary position of gaze the intraocular pressure of the right eye measures 17 mm Hg.

limited duction in a case of strabismus is caused by restriction.<sup>1</sup> This test requires good patient cooperation and an experienced examiner to interpret it. Differential intraocular pressure can be used as an objective, indirect way to demonstrate the presence of restriction.<sup>2</sup> In our experience this is facilitated with the use of the Tono-Pen. Its advantages include a small tip and easy maneuverability, which allows measurement of the intraocular pressure in extreme positions of gaze. The intraocular pressure is measured in primary position and compared with the measurement while the eye attempts rotation into its limited field of gaze. An increase in the intraocular pressure of more than 5 mm Hg suggests that a healthy muscle has



**Fig. 2** (Muñoz and Capó). The intraocular pressure of the right eye increased to 28 mm Hg as the patient attempted to look in the limited field of gaze, up and to the right, suggesting a tight right inferior rectus muscle.



contracted against a tight antagonist muscle or surrounding tissues. This induces compression of the globe and increased intraocular pressure. This test is useful in thyroid ophthalmopathy (Figs. 1 and 2), orbital floor fractures, and strabismus after orbital or retinal detachment surgery.

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### Corneal Autografts for External Knots In Transsclerally Sutured Posterior Chamber Lenses

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Transsclerally sutured posterior chamber lenses at the time of penetrating keratoplasty for pseudophakic bullous keratopathy have been placed as an alternative to anterior chamber and iris sutured posterior chamber lenses.<sup>1</sup> Erosions of transscleral polypropylene suture knots through conjunctiva alone, and through scleral flaps under conjunctiva have been observed.<sup>2-4</sup> The exposure of this suture creates a potential direct pathway for organisms or epithelial downgrowth to the interior of the eye. Endophthalmitis has been reported twice in the setting of transsclerally sutured implants and eroded 9-0 polypropylene suture knots.<sup>3,4</sup> The suture knot eroded through a scleral flap and overlying conjunctiva six years after surgery in one case.<sup>3</sup> In the second case, the knot eroded through conjunctiva alone five months postoperatively.<sup>4</sup>

An exposed suture is also at risk for inadvertent postoperative manipulation and breakage by those not yet familiar with this relatively

new surgical procedure. Fibrosis of haptics to the ciliary body has not been observed.<sup>2</sup> Positioning of the haptics in the ciliary sulcus is frequently not achieved.<sup>2</sup> A case has been reported in which the transscleral implant fell into the vitreous cavity after the external fixation suture was cut at the time of surgical removal secondary to epithelial downgrowth.<sup>2</sup> Thus, the integrity of the fixation sutures is essential to ensure proper support and positioning of these implants.

We have used an alternative surgical technique to address the complication of eroded transscleral sutures. Half-thickness corneal autografts are used to cover the polypropylene knots present on bare sclera. The patient's own corneal button, removed earlier in the procedure, is the source of these patch grafts. A trephine, 2.5 mm in diameter, is used to excise two full-thickness grafts from the larger recipient corneal button. Each graft is split at the midstromal level. The posterior half of the graft with Descemet's membrane facing upward is placed on bare sclera over the 10-0 polypropylene knot. The autograft is sutured to the sclera with two small interrupted 10-0 nylon sutures. The conjunctiva from the adjacent peritomy is placed over the patch graft and secured at the corneoscleral limbus (Figure). In one patient, the autografts were successfully secured over the Prolene knots by using fibrin tissue glue formulated from commercially prepared thrombin and cryoprecipitate obtained from the patient's own blood.

We have performed this technique in eight



**Figure** (Bucci, Holland, and Lindstrom). Corneal autograft secured with two 10-0 nylon sutures covers a transscleral protein suture knot eight months postoperatively.



patients. Follow-up ranged from four to 15 months. Migration of the autograft, erosion of the polypropylene suture, and the formation of dellem has not occurred. No acute or late inflammatory reactions have been observed and all autografts have remained clear. A marginal degree of thinning of the autograft occurred during the first month postoperatively. By the second month, moderate amounts of vascularization were at the base of the autograft (Figure).

Potential advantages of this procedure include the following: (1) A durable barrier and tissue mass is provided by Descemet's membrane and corneal stroma. (2) The perfect immunologic match of the autograft provides no foreign antigens to incite rejection of the transplant. (3) The status of the polypropylene knot can be continuously monitored through the clear autograft. (4) The need to raise scleral flaps is avoided. (5) A patch graft is used without the inconvenience of obtaining tissue from the Eye Bank.

This technique can be used as the surgeon's primary method of guarding against eroded Prolene sutures at the time of penetrating keratoplasty and transsclerally sutured lens implants. Alternatively, the selective use of these autografts has been effective in eyes with excessive perilimbal scarring from previous surgical procedures. The formation of anatomically sound scleral flaps in these eyes has frequently been difficult.

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### Correspondence

Correspondence concerning recent articles or other material published in *THE JOURNAL* should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

### The Elastic Properties of the Lens Capsule in Capsulorhexis

EDITOR:

In the article, "The elastic properties of the lens capsule in capsulorhexis," by E. I. Assia, D. J. Apple, J. C. Tsai, and E. S. Lim (*Am. J. Ophthalmol.* 111:628, May 1991), the authors present a convincing case for optimizing the size of the capsulorhexis on the basis of the method of cataract removal. They also document the possibility of avoiding relaxing incisions when using capsulorhexis for planning extracapsular cataract extraction. We wish to emphasize the importance of corneal magnification at the anterior capsular plane when measuring the anterior capsular opening in vivo during cataract surgery.

All measurements of the anterior capsule described in the article are made after removal of the cornea. The anterior capsule is magnified approximately 1.15 times when viewed through the normal cornea. A capsulectomy that appears 7.0 mm in diameter during surgery would be only 6.1 mm in diameter if directly measured, as described in the article. Although the error would be proportionally less for smaller openings, the authors' data suggest there would be an increased likelihood of complications by not accounting for this magnification when creating the anterior capsulectomy. We make this point to enhance the transfer of the important information contained in this article to everyday application. We congratulate the authors on their approach to this important topic.

KEVIN L. WALTZ, M.D.  
MELVIN L. RUBIN, M.D.  
Gainesville, Florida

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**Reply**

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EDITOR:

We thank Drs. Waltz and Rubin for their comments concerning our article. The laboratory measurements of capsulectomy size were indeed direct measurements of lenses of human eyes obtained post mortem and the corneal magnification of 1.15 times was not considered. We agree that this magnification should be taken into consideration during clinical operations when precise sizing of the anterior capsular opening is required.

EHUD I. ASSIA, M.D.

DAVID J. APPLE, M.D.

JULIE C. TSAI, M.D.

EDWARD S. LIM, M.D.

*Charleston, South Carolina*


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**Herpes Simplex Dendritic Keratitis  
After Keratoplasty**

EDITOR:

In the article, "Herpes simplex dendritic keratitis after keratoplasty" by M. J. Mannis, R. D. Plotnik, I. R. Schwab, and R. D. Newton (*Am. J. Ophthalmol.* 111:480, April 1991), three patients who had no history of herpetic disease developed herpes simplex viral keratitis between three and 11 months after penetrating keratoplasty. The authors concluded that herpes simplex may cause late-onset epithelial defects after keratoplasty even in the absence of a history of herpes simplex keratitis. Results from our laboratory and clinical studies support their findings. We reported that early-onset, as well as late-onset, epithelial defects after keratoplasty may be caused by a herpes infection; unfortunately, the authors failed to cite our investigations.

In our Letter to THE JOURNAL, "Herpes simplex virus and persistent epithelial defects after penetrating keratoplasty," (*Am. J. Ophthalmol.* 109:95, January 1990), we described a patient with no history of herpes keratitis who developed a persistent paracentral, geographic, epithelial defect involving the donor-recipient interface immediately after keratoplasty. The defect was present on postoperative day 1, re-

mained essentially unchanged for two weeks, and did not heal completely until four weeks postoperatively. Ocular herpes cultures were obtained on postoperative days 1, 2, 6, and 15. Two separate cultures obtained on the sixth day were positive for herpes simplex virus.

Nearly 40 years ago, Carton and Kilbourne<sup>1</sup> associated reactivation of latent herpes simplex in humans with surgical trauma. Since the cornea is highly innervated principally by fibers originating in the trigeminal ganglion, we postulated that corneal nerve damage from keratoplasty would similarly reactivate latent virus and result in postkeratoplasty herpes simplex keratitis.<sup>2,3</sup> Using the rabbit we demonstrated that autograft penetrating keratoplasty in conjunction with postoperative corticosteroids significantly increased herpes ocular shedding, epithelial ulceration, and stromal keratitis.<sup>3</sup> In this model, viral shedding and large, geographic, epithelial defects appeared during the first 14 days after keratoplasty. Dendritic lesions and stromal keratitis appeared 26 to 82 days after surgery. We concluded that the surgical trauma from keratoplasty immediately precipitated viral shedding in the tear film, which resulted in early corneal infection and persistent geographic epithelial defects. We further postulated that the herpetic corneal lesions observed weeks to months later may be the result of regenerating corneal nerves that serve as a conduit for the passage of infectious virus from the site of ganglionic latency to the cornea. Therefore, viral reactivation may occur during two periods after keratoplasty: early (days after surgery), as observed in our patient, and late (weeks to months after surgery), as observed by Mannis and colleagues. In the rabbit model, oral acyclovir prophylaxis was effective in reducing herpes simplex virus recurrences after keratoplasty.<sup>4</sup> In rabbits harboring latent virus, positive cultures coincided with herpetic geographic ulcers only 29% of the time.<sup>5</sup> Multiple cultures, as well as other diagnostic aids such as ELISA, immunofluorescence, and immunoperoxidase studies, may be needed to establish the diagnosis.

CRAIG F. BEYER, D.O.  
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JAMES M. HILL, Ph.D.

THOMAS J. BYRD, M.D.

HERBERT E. KAUFMAN, M.D.  
*New Orleans, Louisiana*



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### Reply

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#### EDITOR:

We appreciate the comments of Drs. Beyer, Hill, Byrd, and Kaufman. Their work has significantly contributed to our understanding of herpes simplex keratitis. Indeed, their studies have helped elucidate the role of surgical trauma, corneal nerve disruption, corticosteroids, and antivirals such as acyclovir in the reactivation of latent herpes simplex and the development of keratitis. The patients in our study differed from those described in previously published reports in several respects. Our patients had no known history of previous herpes simplex keratitis. Their epithelial defects developed in the late postoperative period, not in the immediate or early postoperative period. Further, only one of three of the patients was receiving intensive topical corticosteroids for graft rejection. The other two were receiving maintenance doses of topical corticosteroids. The purpose of our study was to emphasize the importance of considering herpes simplex keratitis in the differential diagnosis of late-onset epithelial defects after keratoplasty, even in the absence of a history of herpes simplex keratitis. We agree that corneal and conjunctival cultures as well as other diagnostic aids such as immunofluorescence may be extremely

helpful in the evaluation of both early and late nonhealing epithelial defects after keratoplasty.

MARK J. MANNIS, M.D.  
RONALD D. PLOTNIK, M.D.  
IVAN R. SCHWAB, M.D.  
R. DALE NEWTON, B.A.  
*Sacramento, California*

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### Prevalence of Lattice Degeneration and its Relation to Axial Length in Severe Myopia

#### EDITOR:

In the article, "Prevalence of lattice degeneration and its relation to axial length in severe myopia," by J. M. Celorio and R. C. Pruett (*Am. J. Ophthalmol.* 111:20, January 1991), the authors mention that areas of lattice degeneration frequently show a fishbone or cross-hatch pattern. In the older, European literature, lattice degeneration without a fishbone pattern was referred to as "snail-track degeneration," which aptly compared its appearance to the glistening slime trail left by a passing snail. It is a pity that snail-track and lattice (fishbone) degenerations are considered as a single entity in discussions of chorioretinal lesions associated with retinal detachment.

Snail-track degeneration is a common finding in young myopic individuals, which frequently disappears with advancing age. It seems to be less frequently associated with retinal detachment than is lattice (fishbone) degeneration, but there are no figures in the literature to substantiate or repudiate this impression. Could the authors provide a breakdown of the prevalence of snail-track and of lattice (fishbone) degenerations in relation to axial length and age?

STANLEY HYAMS, M.D.  
*Haifa, Israel*

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### Reply

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#### EDITOR:

Schepens<sup>1</sup> coined the term "lattice degeneration" in 1952. After more than 30 years of additional observation, it was his opinion that "There is scant clinical or pathologic evidence

in favor of classifying snail track degeneration as a separate type or degeneration."<sup>2</sup> Further, in the XXX Edward Jackson Memorial Lecture, Straatsma and associates<sup>3</sup> indicated that retinal alterations described as snail-track degeneration or blood-vessel network degeneration were considered variations of a single disease. The current literature still fails to provide data to support the notion that snail-track and more typical lattice lesions are distinct retinal degenerations rather than different aspects of the same pathologic process.

In our own investigation, we looked for the classical cross-hatched vessel pattern. In other quasi lesions without cross-hatching (snail track) were found in the same fundus, they were counted as lattice. Our statistics did not separate the two. Schepens<sup>2</sup> believed that snail-track defects could represent an early stage of lattice degeneration.

Regardless of the precision of the definition, our data suggested that the prevalence of lattice, and lattice-like lesions, was not directly correlated with the degree of axial myopia. Its frequency appeared to decline in extremely myopic eyes. A population-based study is needed to confirm or deny this observation.

JOSÉ M. CELORIO, M.D.

*Mexico City, Mexico*

RONALD C. PRUETT, M.D.

*Boston, Massachusetts*

after an inferior iridectomy," by E. Bartov, R. Huna, I. Ashkenazi, S. Melamed, I. Gutman, N. Naveh, and G. Treister (*Am. J. Ophthalmol.* 111:501, April 1991), the authors suggested two preventive measures. The first was the creation of a small basal iridectomy. The second was the postoperative positioning of the patient face down. We agree with these measures; however, we have found another approach to be most effective.<sup>1</sup> The method consists of injecting balanced salt solution into the anterior chamber angle at low intraocular pressure; the balanced salt solution remains trapped anteriorly and the silicone oil does not fill the anterior chamber. In this way, the iridectomy is kept free of oil, and the aqueous behind the iris passes freely through the iridectomy and out the trabecular meshwork. Using this technique in 30 cases we have avoided silicone oil pupillary block. In all but one case, this technique was used after the direct exchange of ocular fluid with silicone oil. We believe this is the best preventive measure for early postoperative silicone oil pupillary block glaucoma.

MICHAEL J. SHAPIRO, M.D.

KENNETH I. RESNICK, M.D.

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## Identification, Prevention, and Treatment of Silicone Oil Pupillary Block After an Inferior Iridectomy

EDITOR:

In the article, "Identification, prevention, and treatment of silicone oil pupillary block

## Reply

EDITOR:

The technique recommended by Drs. Shapiro and Resnick, as proposed by Dr. Zivojnovic,<sup>1</sup> is no doubt effective in preventive early postoperative pupillary block. Our experience suggests, however, that in some cases leaving low intraocular pressure in the eye after injection of silicone oil will result in there not being enough silicone oil present in the eye to ensure an effective tamponade, especially in the inferior part of the retina.

We fill the eye with silicone oil until the pressure is moderately increased (20 to 30 mm Hg). Following our strict adherence to the recommendation in our article, we did not have any new cases of silicone oil pupillary block and no cases of shallow anterior chamber because of excess silicone oil in the eye.

On the basis of this experience, we maintain our recommendations for early, face-down po-



sitioning and a small peripheral inferior iridectomy.

ELISHA BARTOV, M.D.  
RUTH HUNA, M.D.  
ISAAC ASHKENAZI, M.D.  
SHLOMO MELAMED, M.D.  
ISAAC GUTMAN, M.D.  
NAVA NAVEH, M.D.  
GIORA TREISTER, M.D.  
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## Scleritis and Wegener's Granulomatosis in Children

### EDITOR:

In the article, "Scleritis and Wegener's granulomatosis in children," by R. D. Sacks, E. L. Stock, S. E. Crawford, M. J. Greenwald, and R. B. O'Grady (*Am. J. Ophthalmol.* 111:430, April 1991), the diagnosis was ultimately confirmed with appropriate histopathologic examination.

We have found serologic examination for antineutrophilic cytoplasmic antibody to be useful when examining patients with scleritis and orbital pseudotumor. Although there is no substitute for a histologically established diagnosis, this serologic test was extremely helpful in leading to the correct diagnosis in our two reported cases.

Antineutrophilic cytoplasmic antibody is a serum test that detects IgG antibodies against cytoplasmic components of neutrophils and monocytes.<sup>1</sup> The test has a high specificity and sensitivity for Wegener's granulomatosis.<sup>2,3</sup> The incidence of false-positive results is low.<sup>3,4</sup> The test is also of great help in monitoring disease activity and treatment response.<sup>2,3</sup> Most of the studies on this test have been published in nonophthalmic literature so a small number of ophthalmologists are aware of its existence and clinical applications.

PAUL H. KALINA, M.D.  
JAMES A. GARRITY, M.D.  
*Rochester, Minnesota*

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## A Magnetic Resonance Imaging Study of the Upshoot-Downshoot Phenomenon of Duane's Retraction Syndrome

### EDITOR:

In the article, "A magnetic resonance imaging study of the upshoot-downshoot phenomenon in Duane's retraction syndrome," by J. N. Bloom, E. R. Graviss, and P. G. Mardelli (*Am. J. Ophthalmol.* 111:548, May 1991), the authors confirmed that the horizontal recti muscles show little, if any, change in their position relative to the medial and lateral orbital walls as the globe elevates or depresses. The authors conclude from these observations that the bridle-effect theory, which has been offered to explain the upshoots and downshoots of the adducted eye in certain patients with Duane's syndrome,<sup>1</sup> must be modified. In my opinion, they have actually provided further evidence that the bridle-effect theory is correct and needs no modification.

Because the horizontal recti muscles maintain their vertical position with reference to the orbital walls, the globe must slip beneath these muscles as it elevates and depresses. Elevation of the eye will move the center of rotation of the globe below the planes of the horizontal recti muscles, whereas depression of the eye will move this center above the muscle planes.<sup>2</sup> It follows that when the eye is only slightly elevated or depressed from the pri-

mary position, a co-contraction of these muscles as it occurs in certain types of Duane's syndrome on adduction will add the functions of elevation or depression to the horizontal action of these muscles. This has been called the bridle or leash effect and causes the upshoot or downshoot of the adducted eye.

Upshoot and downshoot in Duane's syndrome can be improved or eliminated by retro-equatorial scleral fixation of the horizontal recti muscles, by their recession or by splitting the insertion of the lateral rectus muscle, which supports the correctness of the bridle-effect theory because any of these procedures will decrease the vertical shift of the center of rotation with respect to the planes of the horizontal recti muscles during elevation or depression of the eye.

GUNTER K. VON NOORDEN  
Houston, Texas

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### Reply

EDITOR:

We are puzzled by Dr. von Noorden's objection to our recommendation that the bridle-effect theory be modified to account for the minimal vertical displacement of the lateral rectus muscle on both upshoot and downshoot, which we detected in our magnetic resonance imaging study. In the article by von Noorden and Murray,<sup>1</sup> which we cite in our article, the authors state: "To be precise, it is actually the globe that slips beneath the muscle and not, as is commonly assumed, the muscle that slips across the globe." This statement is a modification of the bridle-effect theory. In the illustrations accompanying the discussions

of the bridle-effect theory by Souza-Dias,<sup>2</sup> Scott,<sup>3</sup> and Jampolsky<sup>4</sup> the lateral rectus muscle is shown to slip across the globe, relative to the orbit. Our investigation demonstrated that there was minimal vertical movement of the muscle, in relation to the orbit, and that von Noorden and Murray's proposed modification of the original bridle-effect theory was correct.

Additionally, if only "certain patients with Duane's syndrome" manifest an upshoot or downshoot on adduction, as stated by Dr. von Noorden, then it is difficult to understand why the bridle-effect theory "needs no modification." If co-contraction of the horizontal recti muscles, on attempted adduction, occurs in all patients with Duane's syndrome,<sup>5</sup> then why is an upshoot or downshoot in adduction not a universal phenomenon of this disorder, as would be predicted by the current formulation of the bridle-effect theory?

We believe that modifications of this theory, beyond that proposed in our article, are yet to come.

JEFFREY N. BLOOM, M.D.  
E. RICHARD GRAVISS, M.D.  
PIERRE G. MARDELLI, B.S.  
St. Louis, Missouri

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## BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

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**Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4., Vol. 4.** By Neil R. Miller. Baltimore, Williams & Wilkins, 1991. 2,820 pages, index, illustrated. \$150

Reviewed by NANCY M. NEWMAN  
*Mill Valley, California*

"Magisterial" is no longer the right word for these volumes; "monumental" is more like it. Thus far there are about 900 illustrations and 10,000 references in this major repository of neuro-ophthalmologic information.

This fourth volume in the set is entitled "Vascular Lesions and Circulatory Disorders of the Nervous System." Even this broad-sweeping title does not do justice to the panoply of vascular and blood-vessel-related problems that are considered. The seven chapters are as follows: The Anatomy and Physiology of the Cerebral Vascular System, Aneurysms, Carotid-Cavernous Sinus Fistulas, Cerebrovascular Disease, Migraine, Vasculitis, and Venous Occlusive Disease; all as they apply to the neuro-ophthalmic signs and symptoms seen with these vascular disorders.

As with the other volumes in the set, this volume is an authoritative, exhaustive compilation of clinically relevant material, well written, liberally illustrated, and thoroughly referenced.

One may quibble about whether all the details and illustrations are needed. Taken together, the two volumes on the visual afferent pathways and the various oculomotor systems, including the orbit and the autonomic nervous, are no bigger than this one. The wealth of information in this volume is organized within the chapter heads by the type and the location of the lesion. This makes it hard to find information about a particular patient who has come to the physician with specific signs and symptoms. Dr. Miller has addressed this problem by adding additional sections on symptoms at the end of some chapters.

As in the other volumes, the somewhat spotty index does the author, the publisher, and the reader a major disservice. A weak index is especially exasperating because there is obviously so much information hidden in these volumes.

Again, as with its predecessors, volume 4 of Neil Miller's "Walsh and Hoyt" will be a defini-

tive work and the indispensable reference source in neuro-ophthalmology for years to come; it is a praiseworthy accomplishment.

All readers with a strong interest in neuro-ophthalmology will require this book on their shelves, as will as many other ophthalmologists, neurologists, neurosurgeons, and vascular surgeons. Others in the many areas of medicine into which this volume projects its light will also want to have it at hand.

**Immediate Eye Care.** By Nicola K. Ragge and David L. Easty. St. Louis, Mosby-Year Book, 1990. 228 pages, index, illustrated. \$89

Reviewed by LAWRENCE A. GANS  
*St. Louis, Missouri*

This text is for general practitioners and emergency-care physicians who require a manual of eye diseases and injuries together with a description of their short-term management. The authors have produced a book that is both readable and useful as a quick reference. Medical students will find it helpful as an introduction to eye care and also valuable for later use in general practice. Three major sections comprise the 288 pages of this work. The first section, which briefly reviews the eye examination, begins with a glossary of ophthalmic terms. The next 150 pages devoted to eye diseases are organized by the various structures of the eye and adnexa. The third section consists of chapters dealing with neuro-ophthalmology, trauma, occupational diseases, drug-induced ocular diseases, contact lenses, and other subjects. The text is organized so that each major condition or disease is given a general description followed by the significant signs and symptoms, differential diagnosis, and management. On the basis of the degree of skill required to evaluate and treat the condition, each topic is keyed for the family practitioner or emergency-care physician, the ophthalmology resident, or the ophthalmologist.

The strength of this book lies in the many excellent photographs as well as the high-quality drawings by Terry Tarrant, which complement the text throughout. The index is good for locating subjects for quick reference, and the

structure of the text allows easy understanding of urgent management principles.

Less helpful are the inconsistent use of common medications and the lack of tables listing the available preparations of agents used in short-term eye care. While this may avoid listing agents that are not available outside the United Kingdom, it leaves the reader uncertain as to the appropriate care of certain conditions. For example, the authors state that an infected sebaceous cyst "should be treated with a course of flucloxacillin" instead of just recommending more general treatment with oral antibiotics. The physician treating acute problems has little time to be confused over such things as the use of "0.4% benoxinate" to anesthetize the cornea before culturing rather than the more general description of using a topical anesthetic.

There are also some significant differences in the recommendations for treatment between the standard of care in the United States and the treatment outlined by the authors. For example, in endophthalmitis the authors do not list intravitreal antibiotics as initial treatment, rather stating that these are used after culture results are available. No mention is made of the need for vitrectomy. Other treatment recommendations are too elaborate. Rather than recommending warm compresses, the authors advise treatment of a sty with "hot spoon bathing," which "consists of dipping a wooden cooking spoon wrapped with muslin into boiling water and holding the steaming spoon a few centimeters from the eye (not touching) until the steaming ceases."

For the American reader some of the British terms may be a bit confusing but the superb illustrations and photographs along with the well-organized, succinct text will make this a welcome addition to the general practitioner or emergency-care physician's library.

have existed for over a hundred years, but despite numerous detailed studies there is still lack of agreement on what agnosia tells us about the process of object recognition. More importantly, there is no consensus on the correct classification of agnosic syndromes. Dr. Farah's chief objective is to tackle the taxonomy of agnosia by using a comprehensive review of the existing reports.

The book is divided neatly in two, according to Lissauer's familiar scheme of apperceptive agnosia (abnormalities in complex perceptual processes) and associative agnosia (poor recognition with supposedly intact perception). Two chapters are devoted to each: one reviews the empirical data in case reports, and the other attempts an interpretation of the data with a logical defense of the taxonomy Dr. Farah employs. It quickly becomes clear that a major thrust of her argument is that claims of intact perceptual processes in patients with agnosia, especially with associative agnosia (recalling Teuber's definition of "normal perception stripped of its meaning"), are just not true. Our inability to detect perceptual abnormalities in these patients is more likely a testament to the inadequacy of our tests of vision than to the integrity of their perceptual processes. In Dr. Farah's view, perception and recognition are inseparable elements mediated by distributed processing networks rather than serial elements in a "connectionist" scheme. Thus, she also interprets other more focal syndromes such as pure alexia and prosopagnosia as types of perceptual defects rather than as disruptions of other cognitive or linguistic processes.

Her chapters on interpretation are useful reviews of previous theories of agnosia. The carefully constructed taxonomy is lucidly explained and, most importantly, suggests a number of testable hypotheses for the researcher. While it is unlikely that general ophthalmologists will find much in this book to assist their day-to-day work, anyone with an interest in how vision is achieved will find this a readable and enjoyable monograph. Certainly neuro-ophthalmologists, as the usual consultants of last resort for unexplained or bizarre visual complaints, should at least be familiar with the features of visual agnosia. In that regard, this work is an excellent introduction to a topic that for too long has been a confusing morass of case reports. My own feeling after reading this book was similar to that of returning to my desk and finding that someone had taken a particularly messy drawer and quietly organized its contents into neat, logical folders in my absence.

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**Visual Agnosia.** By Martha J. Farah. Cambridge, Massachusetts, MIT Press, 1990. 184 pages, index, illustrated. \$25

Reviewed by JASON J. S. BARTON  
Toronto, Ontario, Canada

This monograph should serve as a model to anyone who pursues the classic neurologic occupation of deducing function from the study of dysfunction. Descriptions of visual agnosia



**Pediatric Ophthalmology, ed. 3.** Edited by Leonard B. Nelson, Joseph H. Calhoun, and Robison D. Harley. Philadelphia, W. B. Saunders Co., 1991. 532 pages, index, illustrated. \$110

Reviewed by THOMAS D. FRANCE  
*Madison, Wisconsin*

Although it was not the first book to define pediatric ophthalmology, the first edition of Harley's *Pediatric Ophthalmology* was certainly the most comprehensive and the second edition continued in this vein in two volumes. This third edition seems much smaller but continues to cover the wide range of topics necessary to this specialty. In addition to the three editors, there are 30 other contributors, each well qualified to discuss their assigned topic from sensory adaptations in strabismus (Marshall Parks) to pediatric neuro-ophthalmology (Robert Sergott) to uveitis in children (Conrad Giles). The topics of the role of the ophthalmologist in reading disorders (Robert Reinecke) and the ophthalmologist's role with visually impaired children (Marilyn Moller) are especially important.

There have been many changes in pediatric ophthalmology since the last edition was published in 1985. The third edition includes such areas as the new classification of retinopathy of prematurity (1987) and the results of its treatment by cryotherapy (1990), magnetic resonance imaging in orbital and central nervous system disease, optic nerve decompression for chronic papilledema, and a chapter on the genetics of eye disease that relates the great strides made in our understanding of genetic factors in ocular disease. The many tables allow excellent differential diagnoses in each topic, and the complete references listed at the end of each chapter point to further readings. The book is beautifully illustrated with clinical photographs (some in color) and photomicrographs as well as line drawings to aid in identification of disease states and an understanding of pathologic conditions.

This new edition deserves to take its place as a standard in pediatric ophthalmology along with its excellent predecessors.

**Myopia and the Control of Eye Growth.** Edited by Ciba Foundation. Somerset, New Jersey, John Wiley & Sons, 1990. 256 pages, index, illustrated. \$63.50

Reviewed by MARIANETTE MILLER-MEEKS  
*Iowa City, Iowa*

The title of this book summarizes its content. It focuses on the factors that influence eye growth, and hence the pathogenesis of myopia. Professor Wallman's thought-provoking preface highlights the issues that prompted the symposium and primes the reader with some key questions: "If we can figure out why an eye becomes myopic when its vision is blocked (deprivational myopia), will that shed any light on the etiology of school-age myopia, and will that, in turn, lead to an effective preventative treatment for moderate myopia?"

Many of these detailed papers will be hard-going for the average ophthalmologist; however, each paper has a closing summary, and I found the panel discussions to be most valuable.

The volume is rich with references and will be a good place to start looking for the literature on this subject. It is exciting to think we have progressed so far that in the next decades we may not only understand the causes of deprivational myopia, but may also have identified the agents that induce nonpathologic myopia. To be able to prescribe a neurotransmitter, a vitamin supplement, or perhaps an enzyme replacement that reduces or prevents myopia without incising or ablating the cornea is highly desirable, and may soon be within our grasp.

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## Books Received

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**Clinical Tests in Ophthalmology.** By M. J. E. Huber and M. H. Reacher. St. Louis, Mosby-Year Book, 1990. 176 pages, index, illustrated. \$40

Ophthalmologists are forever applying yet another lens or gadget to the patient's eye and peering through some new, ingenious device. Medical students tend to find the instruments intimidating and the tests arcane. The authors of this little book have deliberately, and successfully, set about demystifying the ophthalmic examination, and medical students will be grateful.

**Corneal Angiogenesis: A Comprehensive Critical Review.** By Gordon K. Klintworth. New York, Springer-Verlag, 1991. 135 pages, index. \$59

Among experimental pathologists, Dr. Klintworth is acknowledged as an expert in the area of corneal angiogenesis. This brief volume summarizes his own experience in the subject and reviews the collective literature in the field. The volume is generously referenced (832 references), and is the definitive text for anyone working in this area.

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**Focal Points 1990: Clinical Modules For Ophthalmologists.** San Francisco, American Academy of Ophthalmology, 1990. 12 sections, index. (No price given)

Dr. Tom Shults and his committee, assisted by an able Academy staff, continue to attract useful reviews from various experts and display each one on a few appealing pages. These modules, titled "Focal Points," come out at the rate of about one a month and are a form of continuing education of which the Academy is justly proud.

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**Neurologic Clinics.** Edited by Lenore A. Breen. Philadelphia, W. B. Saunders Company, 1991. 247 pages, index, illustrated. \$79 (per year, individual); \$94 (per year, institution)

Dr. Breen has assembled a dozen reviews of important topics in neuro-ophthalmology that have been receiving recent attention (Lyme disease, idiopathic intracranial hypertension, AIDS, optic neuritis, ischemic optic neuropathy, botulinum toxin therapy, and others). They are presented as glimpses into the field of neuro-ophthalmology for the edification of the

clinician. They are readable, informative, and thought-provoking.

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## The Book List

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**Corneal Angiogenesis: A Comprehensive Critical Review.** By Gordon K. Klintworth. New York, Springer-Verlag, 1991. 135 pages, index. \$59

**Eye Surgery: An Introduction to Operative Technique. Second, Fully Revised, and Expanded Edition.** By Georg Eisner. Translated by Terry C. Telger. New York, Springer-Verlag, 1990. 317 pages, illustrated. \$149

**Eye Trauma.** By Bradford J. Shingleton, Peter S. Hersh, and Kenneth R. Kenyon. St. Louis, Mosby Year Book, Inc., 1991. 427 pages, index, illustrated. \$99

**International Ophthalmology Clinics: Refractive Surgery.** Edited by Gilbert Smolin and Mitchell H. Friedlaender. Boston, Little, Brown & Company, 1991. 111 pages, index, illustrated. \$39

**Retinal Detachment.** By Ronald G. Michels, Charles P. Wilkinson, and Thomas A. Rice. St. Louis, Mosby Year Book, Inc., 1990. 1,138 pages, index, illustrated. \$155

**Strabismus: A Neurodevelopmental Approach.** By John T. Flynn. New York, Springer-Verlag, 1991. 142 pages, index, illustrated. \$65

**Surgical Ophthalmology 1.** Edited by F. C. Blodi, G. Mackensen, and H. Neubauer. New York, Springer-Verlag, 1991. 598 pages, index, illustrated. \$298



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## ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

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**Prevalence of HIV infection in childbearing women in the United States. Surveillance using newborn blood samples.** Gwinn, M.\*, Pappaioanou, M., George, J. R., Hannon, W. H., Wasser, S. C., Redus, M. A., Hoff, R., Grady, G. F., Willoughby, A., Novello, A. C., Petersen, L. R., Dondero, Jr., T. J., and Curran, J. W.: JAMA 265:1704, 1991.

### ACQUIRED IMMUNODEFICIENCY SYNDROME, PREGNANT WOMEN, NEWBORN INFANTS

A national, population-based survey was initiated in 1988 to measure the prevalence of human immunodeficiency virus (HIV) infection in women giving birth to infants in the United States. Following standardized procedures, residual dried-blood specimens collected on filter paper for newborn metabolic screening were tested anonymously in state public health laboratories for maternal antibody to HIV. As of September 1990, annual survey data were available from 38 states and the District of Columbia. The highest HIV seroprevalence rates were observed in New York (5.8 per 1000), the District of Columbia (5.5 per 1000), New Jersey (4.9 per 1000), and Florida (4.5 per 1000). Nationwide, an estimated 1.5 per 1000 women giving birth to infants in 1989 were infected with HIV. Assuming a perinatal transmission rate of 30%, we estimate that approximately 1800 newborns acquired HIV infection during one 12-month period. Preventing transmission of HIV infection to women and infants is an urgent public health priority.—Authors' abstract

\*Technical Information Activity, Division of HIV/AIDS, Mailstop E-49, Centers for Disease Control, Atlanta, GA 30333.

**Trends of HIV seroconversion among young adults in the US Army 1985 to 1989.** McNeil J. G.\*, Brundage, J. F., Gardner, L. I., Wann, F., Renzullo, P. O., Redfield, R. R., Burke, D. S., Miller, R. N., and the US Army Retrovirus Research Group: JAMA 265:1709, 1991.

### HUMAN IMMUNODEFICIENCY VIRUS, UNITED STATES ARMY RECRUITS

Because soldiers in the US Army are recurrently tested for the presence of antibody to the human immunodeficiency virus (HIV), HIV seroconversion rates can be directly measured. From November 1985 through October 1989, 429 HIV seroconversions were detected among 718,780 soldiers who contributed 1,088,447 person-years of follow-up time (HIV seroconversion rate, 0.39 per 1,000 person-years). Period-specific seroconversion rates declined significantly, from 0.49 per 1,000 person-years (November 1985 through October 1987) to 0.33 per 1,000 person-years (November 1987 through October 1988) to 0.29 per 1,000 person-years (November 1988 through October 1989). The HIV seroconversion risk among active-duty soldiers was significantly associated with race/ethnic group, age, gender, and marital status. Based on these trends, we estimate that approximately 220 soldiers (95% confidence interval, 160 to 297 soldiers) were infected with HIV during 1989 and 1990, with potentially fewer in future years.—Authors' abstract

\*Division of Preventive Medicine, Department of Epidemiology, Walter Reed Army Institute of Research, Washington, DC 20307-5100.

**Clinical use of the 193-nm excimer laser in the treatment of corneal scars.** Sher, N. A.\*, Bowers, R. A., Zabel, R. W., Frantz, J. M., Eiferman, R. A., Brown, D. C., Rowsey, J. J., Parker, P., Chen, V., and Lindstrom, R. L.: Arch. Ophthalmol. 109:491, 1991.

### EXCIMER LASER, SUPERFICIAL CORNEAL SCARS

Keratotomy was performed with a 193-nm excimer laser on 33 patients who had corneal opacities with or without irregular astigmatism. The corneal scarring was caused by inactive herpes keratitis, anterior corneal dystrophies, recurrent erosions, granular dystrophy, or band-shaped keratopathy. Most patients received peribulbar anesthetic and underwent

removal of the corneal epithelium was removed before laser ablation. Most individuals had a reduction in the amount of corneal scarring and approximately 50% had improved visual acuity. No intraocular reaction or changes in corneal endothelial counts were observed. Some patients did not need penetrating keratoplasty. Re-epithelialization usually developed within four or five days and no remarkable scarring developed because of the laser. A hyperopic shift secondary to corneal flattening was encountered in approximately 50% of the patients. The 193-nm excimer laser is an effective tool for the treatment of patients with superficial corneal opacities.—Michael A. Kass

\*Phillips Eye Institute, 2215 Park Ave., Minneapolis, MN 55404.

**Long-term results of keratoepithelioplasty in Mooren's ulcer.** Kinoshita, S.\*, Ohashi, Y., Ohji, M., and Manabe, R.: *Ophthalmology* 98:438, 1991.

#### MOOREN'S ULCER, KERATOEPITHELIOPLASTY

Mooren's ulcer is a painful and destructive process that involves the peripheral cornea of one or both eyes. Twenty eyes with Mooren's ulcer were treated by a new surgical approach, which the authors named keratoepithelioplasty. In this technique, the conjunctiva and subconjunctival tissue near the ulcerated cornea were excised. Unhealthy corneal tissue was scraped or excised. Lenticules of corneal epithelium from donor eyes were transplanted. In some eyes, lamellar corneal grafts were also performed. Eighteen of 20 eyes (90%) showed complete remission promptly after surgery; the other two eyes also healed after the administration of additional systemic and topical corticosteroids. During the follow-up period (mean, 3.1 years), minor recurrences were observed in five of 20 eyes (25%) during the first six-month period, in none (0%) during the second six-month period, in two (12%) during the third six-month period, and none thereafter. All seven eyes with recurrences were cured by additional corticosteroid treatment, alone or with conjunctival excision, repeat keratoepithelioplasty, or both.—Michael A. Kass

\*Department of Ophthalmology, Osaka University Medical School, 1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan.

**Topical indomethacin for vernal keratoconjunctivitis.** Gupta, S.\*, Khurana, A. K., Ahluwalia, B. K., and Gupta, N. C.: *Acta Ophthalmol.* 69:95, 1991.

#### VERNAL KERATOCONJUNCTIVITIS, INDOMETHACIN EYEDROPS

Vernal keratoconjunctivitis can be a difficult condition to treat successfully despite the availability of a variety of pharmacologic agents. Twenty-five consecutive children with severe bilateral vernal keratoconjunctivitis were treated with 1% indomethacin eyedrops three times daily. All patients had stopped previous medication for a period of seven days before treatment was initiated. Twenty-one of the 25 patients (84%) improved substantially with indomethacin treatment. Most patients showed some evidence of improvement after only two days and the majority continued to improve over a treatment period of three to five weeks. The efficacy of orally administered aspirin in vernal keratoconjunctivitis has been reported previously. However, indomethacin, which can be applied topically to the eye, has obvious advantages for this condition.—Michael A. Kass

\*10/8 FM, Medical Enclave, Rohtak-124 001, Haryana, India.

**Astigmatism after small incision cataract surgery. A prospective, randomized, multicenter comparison of 4- and 6.5-mm incisions.** Steinert, R. F.\*, Brint, S. F., White, S. M., and Fine, I. H.: *Ophthalmology* 98:417, 1991.

#### CATARACT EXTRACTION, INCISION SIZE, POSTOPERATIVE ASTIGMATISM

Astigmatism and postoperative wound stability were evaluated in a randomized study of 130 patients undergoing cataract extraction. After phacoemulsification through a scleral pocket incision, patients received either a 6.5-mm diameter silicone optic posterior chamber intraocular lens folded for insertion through a 4.0-mm incision or a 6.0-mm diameter polymethylmethacrylate optic posterior chamber intraocular lens placed through a 6.5-mm conventional incision. Vector analysis calculations of postoperative-induced keratometric astigmatism for the small incision vs conventional incision



groups were 1.5 diopters vs 3.1 diopters ( $P < .001$ ) at day 1; 1.0 diopter vs 2.4 diopters ( $P < .001$ ) at weeks 1 to 2; 1.0 diopter vs 1.4 diopters ( $P = .004$ ) at one month; and 0.8 diopters vs 1.0 diopters ( $P = .1$ ) at three months. Complications in the two groups were comparable. Excellent postoperative visual acuity was observed in all groups regardless of the size of the incision or the method of wound closure.—Michael A. Kass

\*50 Staniford St., Boston, MA 02114.

**The deteriorating administrative efficiency of the U.S. health care system.** Woolhandler, S., and Himmelstein, D. U.\*: *N. Engl. J. Med.* 324:1253, 1991.

#### HEALTH CARE COSTS, ADMINISTRATIVE EXPENSES

In 1983, the proportion of health-care expenditures consumed by administration in the United States was 60% higher than that in Canada and 97% higher than that in Britain. In 1987, health-care administration cost between \$96.8 billion and \$120.4 billion in the United States, amounting to between 19.3% and 24.1% of the total spending on health care. In Canada, between 8.4% and 11.1% of health-care spending was devoted to administration. Administrative costs in the United States increased 37% in real dollars between 1983 and 1987, whereas in Canada costs declined. The proportion of health-care spending consumed by the administration is now at least 117% higher in the United States than in Canada and accounts for about half the total difference in health-care spending between the two nations. If health-care administration in the United States had been as efficient as that in Canada, \$69.0 billion to \$83.2 billion would have been saved in 1987. The authors conclude that the administrative structure of the United States health-care system is increasingly inefficient as compared to that of Canada's national health program. Recent health policies with the avowed goal of improving the efficiency of care have imposed substantial new bureaucratic costs and burdens.—Michael A. Kass

\*Division of Social and Community Medicine, Department of Medicine, Cambridge Hospital, 1493 Cambridge St., Cambridge, MA 02139.

**Beyond the Cruzan case: The U.S. Supreme Court and medical practice.** Lo, B.\*, Steinbrook, R.: *Ann. Intern. Med.* 114:895, 1991.

#### LIFE-SUSTAINING TREATMENT, FAMILY DECISIONS

In a landmark decision, the U.S. Supreme Court affirmed a Missouri ruling that sharply limited family decisions about life-sustaining treatment for incompetent patients. The Court held that the Constitution protects the refusal of life-sustaining treatment by competent patients. For incompetent patients, states may require "clear and convincing" evidence of refusal, specifically for the withdrawal of tube feedings, if such a person were in a persistent vegetative state. The ruling left many clinical questions unanswered, such as whether life-sustaining treatment must be given to terminally ill incompetent patients, whether patients may refuse artificial feedings, and what constitutes clear and convincing evidence of refusal. The decision also has potentially harmful consequences. It may undermine family decision making, encourage cynicism and disregard of the law, and promote defensive medicine. Physicians can minimize such consequences by encouraging patients to provide advance directives, such as the durable power of attorney for health care, by urging legislative action, and by setting national practice standards for decisions regarding incompetent patients.—Authors' abstract

\*Program in Medical Ethics, Rm. C-126, 521 Parnassus Ave., San Francisco, CA 94143-0903.

**Assassins and zealots: Variations in peer review.** Siegelman, S. S.: *Radiology* 178:637, 1991.

#### MANUSCRIPT REVIEW, VARIABILITY OF PEER REVIEW

Radiology reviewers are required to assign numerical grades of 1 to 9 (1 = accept, 9 = reject) in the rating of manuscripts. The mean ratings for the 660 referees who were assigned 10 or more reviews over a 4 ½-year period were analyzed. The mean score was  $4.8 \pm 0.8$ , and 87.4% of reviewers (the mainstream) had ratings of mean  $\pm 1.5$  standard deviations. Categories of reviewers with greater deviation from the mean were identified: zealots and push-

overs, whose ratings of manuscripts were more favorable, versus assassins and demoters, who supplied less favorable ratings. To exclude the possibility that the referees who were classified as more critical had actually been sent less meritorious papers, the scores and rejection rates of 859 papers co-reviewed by assassins, demoters, and mainstream referees were compared. Significant differences were confirmed. Deviant referees were widely distributed in the pool of reviewers, including 13 members of the Editorial Board and representatives in each of 19 subspecialty areas. Failure to recognize and control for reviewer variation may be unfair to authors. An Editor has the capacity to reduce unfairness by monitoring reviewer variation and by modulating the review process accordingly.—Author's abstract

\*Johns Hopkins Medical Institutions, 550 N. Broadway, Ste. 206, Baltimore, MD 21205.

**The hypocholesterolemic effects of  $\beta$ -glucan in oatmeal and oat bran. A dose-controlled study.** Davidson M. H.\*, Dugan, L. D., Burns, J. H., Bova, J., Story, K., and Drennan, K. B.: JAMA 265:1833, 1991.

#### CHOLESTEROL LEVELS, OAT BRAN, OATMEAL

Oat cereals rich in water-soluble fiber  $\beta$ -glucan have been studied as a dietary therapy for hypercholesterolemia. To determine the hypocholesterolemic response of  $\beta$ -glucan in the diet, 156 adults with low-density lipoprotein cholesterol (LDL-C) levels above 4.14 mmol/L (160 mg/dL) or between 3.37 and 4.14 mmol/L (130 and 160 mg/dL) with multiple risk factors were randomized to one of seven groups. Six groups received either oatmeal or oat bran at doses (dry weight) of 28 g (1 oz), 56 g (2 oz), and 84 g (3 oz). A seventh group received 28 g of farina ( $\beta$ -glucan control). At week 6 of treatment, significant differences were found for both total cholesterol and LDL-C levels among the farina control and the treatment groups who were receiving 84 g of oatmeal, 56 g of oat bran, and 84 g of oat bran, with decreases in LDL-C levels of 10.1%, 15.9%, and 11.5%, respectively. Fifty-six grams of oat bran resulted in significantly greater reductions in LDL-C levels than 56 g of oatmeal. Nutrient analysis shows no difference in dietary fat content between these treatment groups; therefore, the

higher  $\beta$ -glucan content of oat bran most likely explains the significantly greater LDL-C reductions. A dose-dependent reduction in LDL-C levels with oat cereals supports the independent hypocholesterolemic effects of  $\beta$ -glucan.—Authors' abstract

\*Chicago Center for Clinical Research, 800 S. Wells, Ste. M-25, Chicago, IL 60607.

**Analyzing hospital mortality. The consequences of diversity in patient mix.** Green J.\*, Passman, L. J., and Wintfeld, N.: JAMA 265:1849, 1991.

#### HOSPITAL MORTALITY, ELDERLY PATIENTS, HIGH-RISK DIAGNOSES

Consumers and payers increasingly demand data with which to evaluate health care providers. While publication of risk-adjusted hospital-specific death rates is one response, debate continues over whether higher than predicted mortality is a warning about quality of care or rather a reflection of a hospital's atypical patient population. To help inform this debate, we compared the characteristics of Medicare patients discharged from 187 hospitals that the Health Care Financing Administration (HCFA) had labeled "high-mortality outliers" with those of Medicare patients from 5373 hospitals not so designated. Hospitals were most likely to be flagged as high-mortality outliers by HCFA when they had large shares of very elderly patients (age  $\geq 85$  years), patients with high-risk diagnoses, or patients requiring nursing home care. After adjustments were made to compensate for these biases, nearly half the hospitals flagged as outliers by HCFA were no longer so designated. Statistics purporting to measure effectiveness of care from hospital death rates should be modified to account for diversity in patient mix.—Authors' abstract

\*Director of Health Policy Research, New York University Medical Center, 550 First Ave., (IRM), New York, NY 10016.

**In-vitro assessment of a hypersensitivity syndrome associated with sorbinil.** Spielberg, S. P., Shear, N. H.\*, Cannon, M., Hutson, N. J., and Gunderson, K.: Ann. Intern. Med. 114:720, 1991.



**SORBINIL, ALDOSE REDUCTASE INHIBITOR, HYPERSENSITIVITY SYNDROME**

Sorbinil is a hydantoin aldose reductase inhibitor that has shown promise as therapy for patients with diabetic complications such as neuropathy and retinopathy. However, as many as 10% of patients receiving sorbinil have had adverse reactions characterized by fever, skin rash, and myalgia. Our previous studies of phenytoin suggested that susceptibility to reactions might result from an inherited detoxification defect. We did the current study to determine if sorbinil is metabolized to reactive intermediates and if cells from patients with a history of a reaction to sorbinil are appropriate for the in-vitro investigation of susceptibility. Microsome-generated metabolites of sorbinil (50  $\mu$ M) were toxic to normal peripheral blood lymphocytes (7.9%  $\pm$  0.3% dead cells [mean  $\pm$  SE]). Toxicity was increased in the presence of an epoxide hydrolase inhibitor (17.5%  $\pm$  0.3% dead cells) and abolished by an inhibitor of cytochrome P-450. In contrast to cells from healthy controls and diabetics who tolerated sorbinil (7.9%  $\pm$  0.7% and 7.8%  $\pm$  0.4% dead cells, respectively), cells from the six patients who had sorbinil reactions showed significantly increased toxicity from metabolites of sorbinil and phenytoin (19.7%  $\pm$  2.3% dead cells,  $P < 0.001$ ). Cells from three patients who had reactions to phenytoin were similarly sensitive to sorbinil metabolites (23.4%  $\pm$  0.3% dead cells). We conclude that sorbinil is oxidatively metabolized to a potentially toxic intermediate. Certain patients may be at increased risk for developing hypersensitivity reactions. Development of this important new drug has been hampered by uncommon but potentially severe reactions. An increased understanding of the steps involved in the development of adverse reactions could lead to screening tests or to the development of safer compounds.—Authors' abstract

\*Division of Clinical Pharmacology, Sunnybrook Health Science Centre A3, 2075 Bayview Ave., Toronto, Ontario, Canada M4N 3M5.

**Visual hallucinations on eye closure associated with atropine toxicity. A neurological analysis and comparison with other visual hallucinations.** Fisher, C. M.\*: *Can. J. Neurol. Sci.* 18:18, 1991.

**VISUAL HALLUCINATIONS, ATROPINE TOXICITY**

A 74-year-old man developed severe bradycardia and was treated with 1.0 mg of atropine intravenously, with an additional 0.6 mg given five hours later. The patient's cardiac function then remained satisfactory, but approximately four hours after the second dose he developed florid, formed visual hallucinations that persisted with decreasing severity for 11 days. The hallucinations were present only when his eyes were closed and were associated with heightened dreaming and disturbed sleep. The hallucinations were similar to hypnagogic hallucinations, which occur during the process of falling asleep or awakening. The author hypothesizes that the hallucinations originated in the sleep-dream system of the brain stem. It is possible that this site or a similar site plays a role in other types of visual hallucinations and delirium.—Michael A. Kass

\*Neurology Service, Massachusetts General Hospital, Boston, MA 02114.

**Prognostic significance of conjugate eye deviation in stroke patients.** Tijssen, C. C.\*, Schulte, B. P. M., and Leyten, A. C. M.: *Stroke* 22:200, 1991.

**ACUTE STROKE, CONJUGATE EYE DEVIATION, MORTALITY AND DISABILITY**

We prospectively studied the prognostic significance of conjugate eye deviation in 80 patients with acute stroke and compared the 3-month mortality and disability of these patients to those of the Tilburg epidemiological study of stroke. Mortality of patients with conjugate eye deviation was higher (41%) than for the general stroke population (34%), but this difference was not statistically significant ( $p < 0.179$ ). Looking at mortality and disability together, we found the outcome of patients with conjugate eye deviation to be significantly worse ( $p < 0.001$ ). Deviation of the eyes occurred more frequently to the right (65%) than to the left (35%). In the patient group with eye deviation to the left, mortality was significantly higher (64%,  $p < 0.001$ ) than in the group with eye deviation to the right (25%); only two patients of the former group ( $n = 28$ ) could return home. Compared to the Tilburg epidemiological study of stroke, the group with eye deviation to the

left did significantly worse, both for mortality alone ( $p < 0.001$ ) and for mortality and disability together ( $p < 0.001$ ). The group with eye deviation to the right did significantly worse only for mortality and disability together ( $p < 0.01$ ). Our results indicate that conjugate eye deviation is a prognostic factor for poor short-term mortality and disability in stroke patients, especially when the eyes are deviated to the left.—Authors' abstract

\*Department of Neurology, St. Elisabeth Hospital, P.O. Box 90151, 5000 LC Tilburg, The Netherlands.

**Prognostic factors in idiopathic preretinal macular fibrosis.** Akiba, J.\*, Yoshida, A., and Trempe, C. L.: Graefes Arch. Clin. Exp. Ophthalmol. 229:101, 1991.

**IDIOPATHIC PRERETINAL MACULAR FIBROSIS, VITREOUS TRACTION, FLUORESCIN LEAKAGE**

The authors reviewed 124 eyes with idiopathic preretinal macular fibrosis to assess the value of fluorescein angiography and vitreous examination for predicting the visual prognosis. During a mean follow-up period of 43 months (range, 12–114 months), the visual acuity of 33 eyes (27%) declined two or more lines from the initial value, although the appearance of the fibrosis remained unchanged in 114 cases (92%). At initial examination, 38 eyes (31%) showed fluorescein leakage into the macula; these eyes were more prone to further visual deterioration than were those without leakage ( $P < .05$ ). Of 14 eyes with partial vitreous detachment and vitreous traction to the fibrosis, six (43%) had a final visual acuity of 20/200 or worse; this proportion was significantly higher than that found either in eyes with no detachment or in those with complete vitreous detachment ( $P < .05$ ). The presence of fluorescein leakage, vitreous traction, or both, to the fibrosis may predict worse functional prognosis in eyes with idiopathic preretinal macular fibrosis.—Michael A. Kass

\*Department of Ophthalmology, Asahikawa Medical College, 4-5 Nishi-Kagura, Asahikawa, 078 Japan.

**Lisch nodules in neurofibromatosis type I.** Lubs, M.-L. E., Bauer M. S.\*, Formas, M. E., and Djokic, B.: N. Engl. J. Med. 324:1264, 1991.

**NEUROFIBROMATOSIS TYPE I, LISCH NODULES**

Lisch nodules are melanocytic hamartomas that appear as yellow to brown, well-defined, dome-shaped elevations projecting from the surface of the iris. Multiple Lisch nodules are common in patients with peripheral neurofibromatosis and are the most common clinical feature of neurofibromatosis type I in adults. A cohort of 167 patients with neurofibromatosis type I underwent careful slit-lamp examination. Only 5% of the children less than 3 years of age had Lisch nodules. The prevalence of nodules increased to 42% among the children 3 to 4 years of age and 55% among the children 5 to 6 years of age. All 65 adults who were 21 years of age or older had Lisch nodules. Thus, slit-lamp examination is a simple, inexpensive, nonevasive procedure that is an important tool in establishing the diagnosis of neurofibromatosis type 1.—Michael A. Kass

\*Miami Children's Hospital, Miami, FL 33155.

**Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism.** Hashizume, K.\*, Ichikawa, K., Sakurai, A., Suzuki, S., Takeda, T., Kobayashi, M., Miyamoto, T., Arai, M., and Nagasawa, T.: N. Engl. J. Med. 324:947, 1991.

**HYPERTHYROIDISM, THYROXINE, RECURRENT HYPERTHYROIDISM**

Hyperthyroidism in patients with Graves' disease is primarily caused by antibodies that bind to receptors for thyroid-stimulating hormone. One factor that might contribute to the persistent production of antibodies to thyroid-stimulating hormone receptors is stimulation of the release of thyroid antigens by thyroid-stimulating hormone during antithyroid drug treatment. The levels of antibodies to thyroid-stimulating hormone receptors were measured during treatment with methimazole, either alone or in combination with thyroxine, in 109 patients with hyperthyroidism caused by Graves' disease. The patients first received 30 mg of methimazole daily for six months. All were euthyroid after six months, and their mean level of antibodies to thyroid-stimulating hormone receptors decreased from  $64 \pm 9\%$  to



25  $\pm$  15%. Sixty patients then received 100  $\mu$ g of thyroxine and 10 mg of methimazole while 49 patients received placebo and 10 mg of methimazole daily for one year. In the thyroxine-treated group, the mean serum thyroxine concentration increased from 108  $\pm$  16 nmol/l to 145  $\pm$  11 nmol/l, and the level of antibodies to thyroid-stimulating hormone receptors decreased from 28  $\pm$  10% to 10  $\pm$  3% after one month of combination therapy. In the patients who received placebo and methimazole, the mean serum thyroxine concentration decreased and the level of antibodies to thyroid-stimulating hormone receptors did not change. The use of methimazole, but not thyroxine or placebo, was discontinued in each group 18 months after the beginning of treatment. The level of antibodies to thyroid-stimulating hormone receptors further decreased from 6.6  $\pm$  3.2% at the time methimazole was discontinued to 2.1  $\pm$  1.2% one year later in the patients who continued to receive thyroxine. In contrast, the level of antibodies to thyroid-stimulating hormone receptors increased from 9.1  $\pm$  4.8% to 17.3  $\pm$  5.8% during the same period in the patients who received placebo. One of the 60 patients in the thyroxine-treated group (1.7%) and 17 of 49 patients in the placebo group (34.7%) had recurrences of hyperthyroidism within three years after the discontinuation of methimazole. The administration of thyroxine during antithyroid drug treatment decreases both the production of antibodies to thyroid-stimulating hormone receptors and the frequency of recurrence of hyperthyroidism.—Michael A. Kass

\*Department of Geriatrics, Endocrinology, and Metabolism, Shinshu University School of Medicine, Matsumoto 390, Japan.

**Mood disorders in patients with chronic simple glaucoma.** Carrieri, P. B.\*, Gentile, S., Fusco, R., and Greco, G. M.: *Psychiatry Res.* 36:233, 1991.

#### OPEN-ANGLE GLAUCOMA, DEPRESSION

Fifteen patients with open-angle glaucoma, 15 patients with diabetic retinopathy, and 15 normal patients were matched for age and gender. All subjects were interviewed between 11:00 A.M. and 1:00 P.M. and underwent a detailed psychiatric assessment. None of the patients or the controls had personal or family history of psychiatric illness and none of the glaucoma patients was receiving a topically applied beta blocker. Twelve of the 15 patients with glaucoma (80%) satisfied DSM-III criteria for depression, three for major depression, and nine for minor depression. Only four of 15 patients (26%) with diabetic retinopathy fulfilled the criteria for minor depression and none for major depression. Only two control subjects (13.3%) showed minor depression. The diabetic patients were comparable in age, gender, disease duration, and visual acuity to the patients with glaucoma. It thus appears that the depression found in the patients with open-angle glaucoma is not merely a psychologic reaction to their having a chronic eye disease.—Michael A. Kass

\*Institute of Neurology, 2nd Medical School, 80131 Naples, Italy.

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## NEWS ITEMS

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**Send News Items to  
American Journal of Ophthalmology  
435 N. Michigan Ave., Suite 1415  
Chicago, IL 60611**

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

**Greek Intra-Ocular Implant & Refractive Surgery Society: 6th Symposium**

The Greek Intra-Ocular Implant & Refractive Surgery Society will sponsor its 6th Symposium, Nov. 15-17, 1991, in Athens. For more information, write Mrs. Irene Pandealeki, Ploutarchou Street 10, Athens 106 76, Greece; fax (01) 7230841.

**Emory University School of Medicine:  
Current Neuro-Ophthalmology**

The Department of Ophthalmology at Emory University School of Medicine will sponsor a conference, "Current Neuro-Ophthalmology," Dec. 6, 1991, at the Ritz-Carlton Buckhead, Atlanta, Georgia. For further information, write Emory University School of Medicine, Continuing Medical Education Dept., 1440 Clifton Rd., Atlanta, GA 30322; telephone (404) 727-5695.

**New York Society for Clinical  
Ophthalmology: Fall Meeting**

The New York Society for Clinical Ophthalmology will hold its Fall Meeting, Nov. 9, 1991, in New York City. For additional information, write Francine Leinhardt, 210 E. 64th St., New York, NY 10021; telephone (212) 838-9200 ext. 2776; fax (212) 832-9126.

**West Virginia University: 12th Annual  
Ophthalmology Clinical Conference**

The Department of Ophthalmology at the West Virginia University will sponsor its 12th Annual Ophthalmology Clinical Conference,

Nov. 1 and 2, 1991, at Lakeview Resort and Conference Center, Morgantown, West Virginia. For more information, write the Department of Ophthalmology, WVU Health Sciences Center North, Morgantown, WV 26506; telephone (304) 293-3757.

**New York Academy of Medicine: New  
Officers**

The Section on Ophthalmology at the New York Academy of Medicine has elected new officers: Ronald M. Burde, M.D., chairman; and Robert Ritch, secretary.

**Chicago Ophthalmological Society:  
1991-1992 Officers**

The Chicago Ophthalmological Society has elected new officers for 1991-1992: Karl W. Scheribel, president; Allen Putterman, vice-president; Elise Torczynski, president-elect; Alan Axelrod, secretary-treasurer; and Robert Schroeder, corresponding secretary.

**New York Society for Clinical  
Ophthalmology: 1991-1992 Officers**

The New York Society for Clinical Ophthalmology has elected officers for 1991-1992: Robert Ritch, president; Frederick M. Wang, chairman, Program Committee; Stanley Chang, chairman, Membership Committee; Thomas O. Muldoon, treasurer; Ronald M. Burde, recording secretary; Dorothy N. Friedberg, correspondence secretary; and Kevin C. Greenidge, historian.

**San Diego County Ophthalmological  
Society: 1991-1992 Officers**

The San Diego County Ophthalmological Society has elected officers for 1991-1992: Paul E. Tornambe, president; John E. Bokosky, vice president; Daniel R. Terhorst, secretary; and David A. Edwards, treasurer.

**National Advisory Eye Council: New  
Members**

Three new members have been appointed to the National Advisory Eye Council who will serve through November 1994. The new members are Argye Hillis, Ph.D., Texas A & M



University, Joseph Horwitz, Ph.D., University of California at Los Angeles, and Paul L. Kaufman, M.D., University of Wisconsin at Madison.

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**Personal**

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**Douglas John Coster**

Douglas John Coster, received the 1991 Lions Clubs International Humanitarian Award at the

Lions International Convention in Brisbane, Australia. Dr. Coster will use the \$250,000 award to further his work in preventive and public health ophthalmology. Dr. Coster is senior director of ophthalmology at Flinders, Australia, Medical Center. He is deputy chairman of the South Australia Health Commission and a Lions professor of ophthalmology at Flinders University.

## INSTRUCTIONS TO AUTHORS

For the preparation of typescripts for **THE AMERICAN JOURNAL OF OPHTHALMOLOGY**

For more detailed information, see the Instructions to Authors published periodically in each volume, or write to Editorial assistant, American Journal of Ophthalmology, Suite 1415, 435 N. Michigan Avenue, Chicago, IL 60611.

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The manuscript must be original and may not contain data published previously or submitted for publication elsewhere. If the data were presented at a scientific meeting, the place, date of presentation, and auspices of the meeting should be stated on the title page.

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Submit an original and at least two duplicate copies of both the typescript and illustrations. Xerographic copies of the typescript are preferred

to carbon copies. The manuscript should be arranged in the following order: title page; summary; text; references; legends; and tables. Each section should begin on a separate sheet.

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The title page is page 1. It should contain the title, a brief heading (no more than 60 characters and spaces) in the upper right hand corner, and each author's name with the highest academic degree. The department and institution where the study was performed should be indicated. Sponsoring organizations and grant support are acknowledged on the title page. The name and mailing address of the author to whom requests for reprints should be directed must be indicated.

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Each paper must have a summary that specifically condenses the content of the paper in 150 words or less. The summary must be written so that the message of the paper can be understood independently. It should include the main clinical or research data and findings but exclude speculation.

### References

The corresponding author is responsible for complete and accurate references, including proper capitalization and accent marks used in foreign-language publications. References must be numbered consecutively, according to their appearance in the text. Extensive bibliographic reviews are not acceptable. The names of all authors must be included; THE JOURNAL does not use the term et al. Index Medicus abbreviations are used. Personal communications and references to studies in progress or not yet accepted for publication must be incorporated into the text without reference numbers.

### Illustrations

Graphs, diagrams, and line drawings must be prepared by a professional artist using India ink.



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Visual field charts used in THE JOURNAL will be supplied to authors without charge upon request. Write to the Editorial Assistant.

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Authors must contribute \$500 per page toward the cost of color illustrations. Color transparencies, professional color prints, and a layout indicating the proposed distribution of the illustrations together with their legends must be submitted with the manuscript.

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Tables must be double spaced. Vertical lines should not be used. Abbreviations must be used only for units of measure.

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CBE Style Manual Committee: Council of Biology Editors Style Manual. A Guide for Authors, Editors and Publishers in the Biological Sciences, ed. 5. Bethesda, Council of Biology Editors, 1983.

The Chicago Manual of Style, ed. 13. Chicago, University of Chicago Press, 1982.

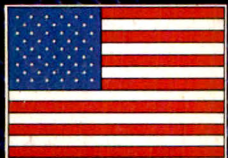
Strunk W., Jr., and White, E. B.: The Elements of Style, ed. 3. New York, Macmillan Publishing Co., 1979.



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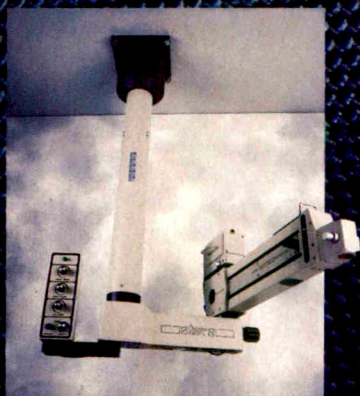
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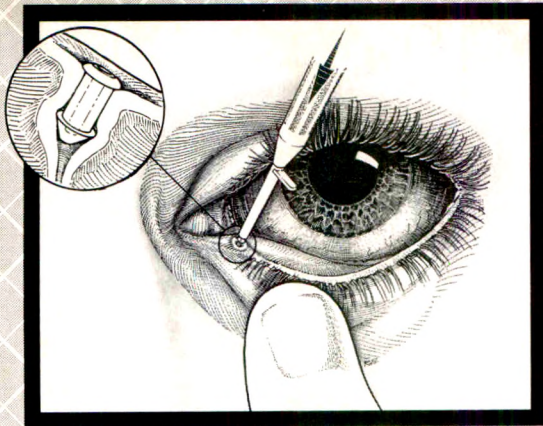


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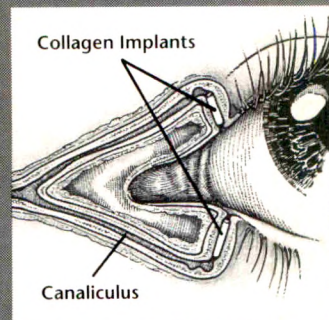
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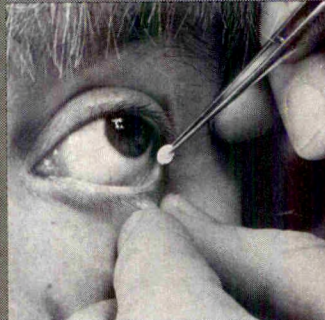
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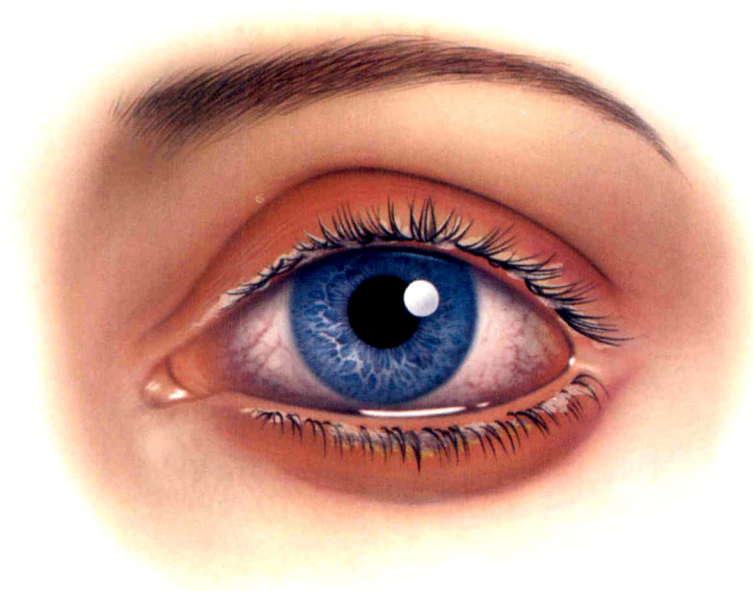
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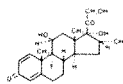
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Chemical Name:

9-Fluoro-11 $\beta$ ,17,21-trihydroxy-16 $\alpha$ -methylpregna-1,4-diene-3,20-dione

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Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

No data are available on the extent of systemic absorption from TOBRADEX Ophthalmic Suspension or Ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. If the maximum dose of TOBRADEX Ophthalmic Suspension is given for the first 48 hours (two drops in each eye every 2 hours) and complete systemic absorption occurs, which is highly unlikely, the daily dose of dexamethasone would be 2.4 mg. The usual physiologic replacement dose is 0.75 mg daily. If TOBRADEX Ophthalmic Suspension is given after the first 48 hours as two drops in each eye every 4 hours, the administered dose of dexamethasone would be 1.2 mg daily. The administered dose for TOBRADEX Ophthalmic Ointment in both eyes four times daily would be 0.4 mg of dexamethasone daily.

**INDICATIONS AND USAGE:** TOBRADEX Ophthalmic Suspension and Ointment are indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

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The use of this combination is always contraindicated after uncomplicated removal of a corneal foreign body.

**WARNINGS:** NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction does occur, discontinue use.

Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

**PRECAUTIONS:****General:** The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.**Information for Patients:** Do not touch dropper or tube tip to any surface as this may contaminate the contents.**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.**Pregnancy Category C:** Corticosteroids have been found to be teratogenic in animal studies. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of fetal anomalies in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy. Reproduction studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. TOBRADEX Ophthalmic Suspension and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, a decision should be considered to discontinue nursing temporarily while using TOBRADEX Ophthalmic Suspension or Ointment.**Pediatric Use:** Safety and effectiveness in children have not been established.**ADVERSE REACTIONS:** Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are isolated ocular toxicity and hypersensitivity, including itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage posterior subcapsular cataract formation, and delayed wound healing.**Secondary Infection:** The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop concomitantly with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.**DOSE AND ADMINISTRATION:** Suspension: One or two drops instilled into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, the dosage may be increased to one or two drops every two (2) hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely. Ointment: Apply a small amount (approximately 1/2 inch ribbon) into the conjunctival sac(s) up to three or four times daily.

TOBRADEX Ophthalmic Ointment may be used at bedtime in conjunction with TOBRADEX Ophthalmic Suspension used during the day. Not more than 20 mL or 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

**HOW SUPPLIED:** Sterile ophthalmic suspension in 2.5 mL (NDC 0065-0647-25) and 5 mL (NDC 0065-0647-05) DROP-TAINER® dispensers.

Sterile ophthalmic ointment in 3.5 g ophthalmic tube (NDC 0065-0648-35).

**STORAGE:** Store at 46° to 80°F (8° to 27°C).

Store suspension upright and shake well before using.

**CAUTION:** Federal (USA) law prohibits dispensing without prescription. Patent pending.**Alcon®**  
OPHTHALMICALCON LABORATORIES, INC.  
Fort Worth, Texas 76134**THE TENTH AFRO-ASIAN  
CONGRESS OF OPHTHALMOLOGY****JULY 17-21, 1992****JAKARTA, INDONESIA****\* MAIN FEATURES:**

prevention of blindness, cataract, vitreo-retinal, glaucoma, immunology, external eye diseases, and corneal surgery.

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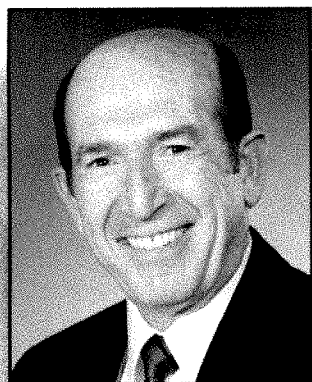
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# Adopting new technology can be frightening; you may want a second opinion . . .

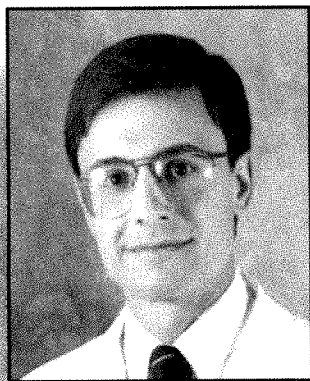


"The Microlase can be used to melt the ends of 10-0 nylon sutures that protrude through conjunctiva following cataract surgery. We use 100 micron spot size, 1.0 Watts, and 0.3 seconds exposure. One pulse is usually adequate to melt the end and cause it to shrivel below the conjunctival surface.

The differential in payment by Medicare for treating diabetic retinopathy in the hospital versus in our office has already paid for our Diode Laser in less than a year. On the two occasions where the Microlase required service, the Keeler Company had us back in operation in 24 hours."

**O. David Solomon, M.D.**  
**Beachwood, Ohio**

  
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"Fully portable and can be set-up in minutes!

From suitcase to slit lamp in a matter of minutes—unbelievable!

An extremely clear view of the retina facilitates photocoagulation."

**Anthony M. Sensoli, M.D.**  
**Chelsea, Michigan**

Dear Dr.

You are one of a very elite group of contemporary Ophthalmologists who with your purchase of a Microlase Diode Laser have incorporated the very latest in laser technology into your practice.

Your comments and conclusions are sought after and in our own experience when demonstrating the Microlase we are always asked by your fellow Ophthalmologists; "who's using it", "what are their comments, opinions", etc. In response to these queries I have enclosed a draft of a new advertisement which we will be placing in the Ophthalmic Journals. This publication is designed to answer many of the questions we are asked, as well as quell some ill founded rumors about the semi conductor diode lasers. We hope to encourage others to include the Microlase in their evaluations of the lasers available today when anticipating the purchase of a new Laser.

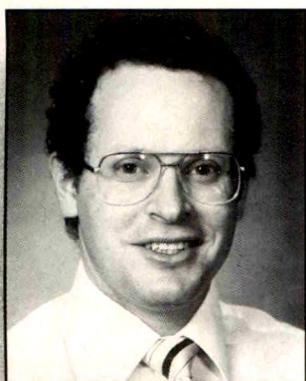
We do not seek your endorsement of Microlase as the *only* choice but rather your comments on how Microlase has added positively to your practice. I hope you will consider being included in this group of truly contemporary Ophthalmologists and I look forward to receiving your photograph and comments.

Sincerely,

  
M. Colleen Lyall  
Vice President, Marketing & Sales

"I consider the Microlase system to be the next step in macular photocoagulation. The comment that I would most like to share with my colleagues is: Diode Laser is the modality of choice in RPE selective photocoagulation. While I have used the diode laser for laser trabeculoplasty and panretinal photocoagulation, RPE selective photocoagulation is the area where there is clear cut superiority to conventional argon laser techniques.

**Brian Harper M.D.**  
**Rockdale, Texas**



"The response of the glaucoma patients to the Diode trabeculoplasty is rapid and dramatic, surpassing anything I have ever seen with the Argon laser.

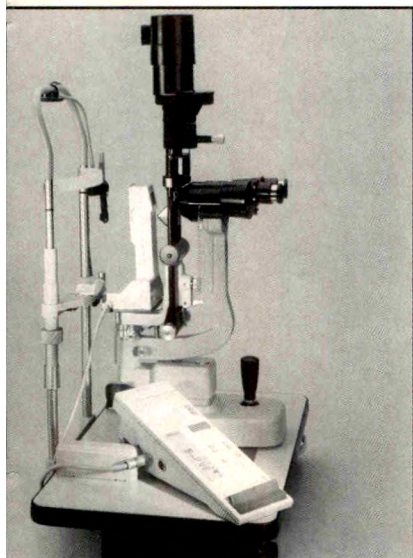
The patients who need retinal work compare the Diode favorably to the Argon, because of the lack of the flash of light and the loud clicking noise.

The convenience of the Diode in the office has paid dividends already. The first day, a subretinal net was treated immediately upon presentation, diagnosis and fluorescein angiography without having to leave the office for the outpatient clinic at the hospital."

**Jon Schmeyer, M.D.**  
**Hanover, Pennsylvania**

"The longer I use the Microlase the more I am impressed with its usefulness. I have used it for glaucoma and I find no significance between the results obtained from the Microlase and the Argon laser. However, the Microlase does not have the same type of end-point as the Argon. I find it very useful in treating retinal lesions, retinal tears, and diabetic retinopathy. I am an enthusiastic user of the Microlase."

**Waite S. Kirkconnell, M.D., F.A.C.S.**  
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For an in-office demonstration and an opportunity to form your own opinion, call Keeler today at  
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The doctors featured in this advertisement have no financial interest in the Microlase system or Keeler Instruments.



# The eyes can be windows to a lot more than the soul.

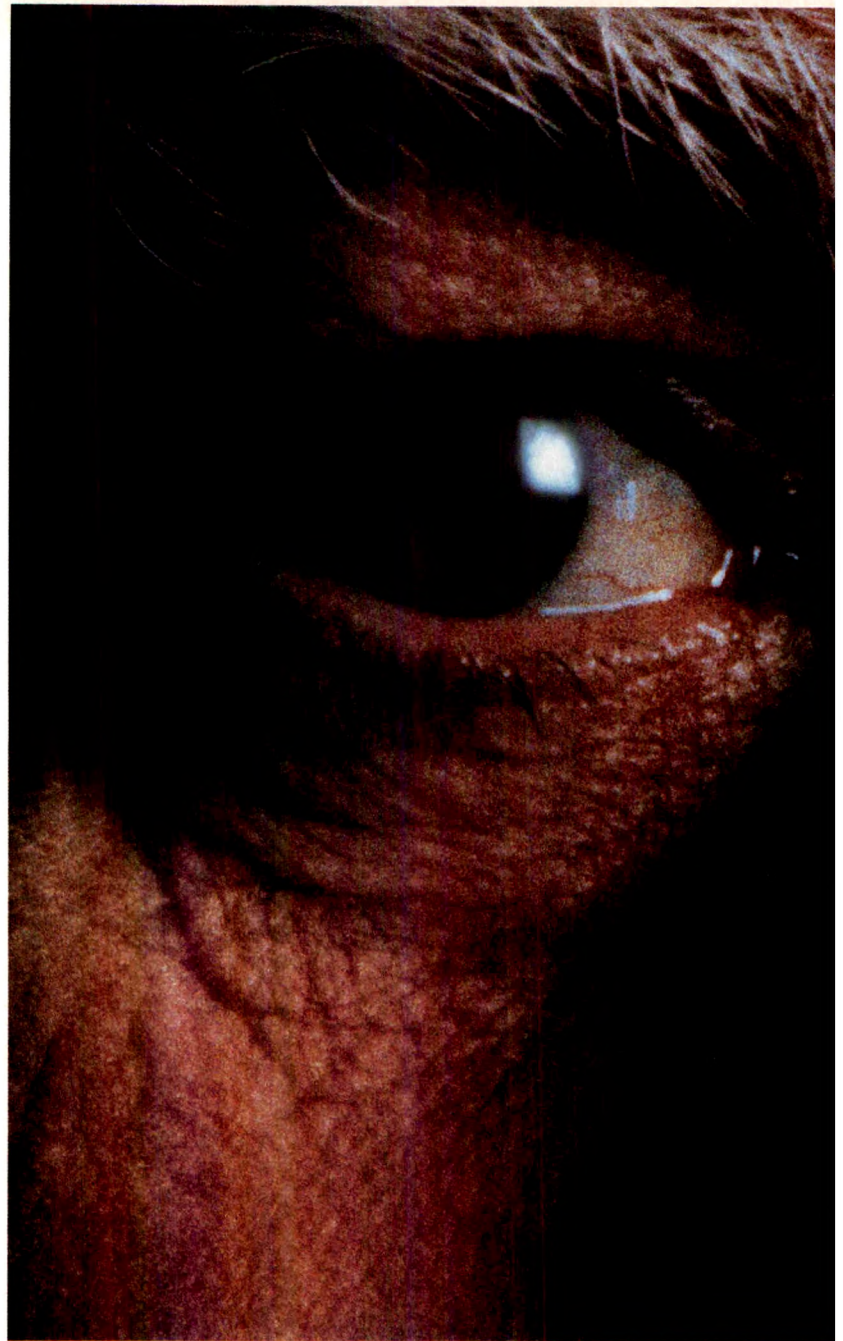
Some of the most poetic passages throughout history have been written about the eyes.

But this isn't one of them.

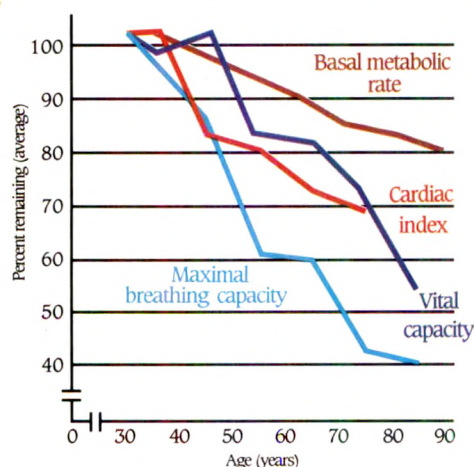
## Ocular beta blockers can affect more than the eyes.

Unfortunate, but true. Minutes after a single dose of an ocular beta blocker, the drug is detectable in the plasma of most individuals.<sup>1</sup>

That's important when you consider that most glaucoma patients are elderly. With age comes a normal decline in physiologic function and increased susceptibility to systemic disease.<sup>2</sup> And concomitant systemic medication increases the likelihood of adverse drug reactions.<sup>2</sup>



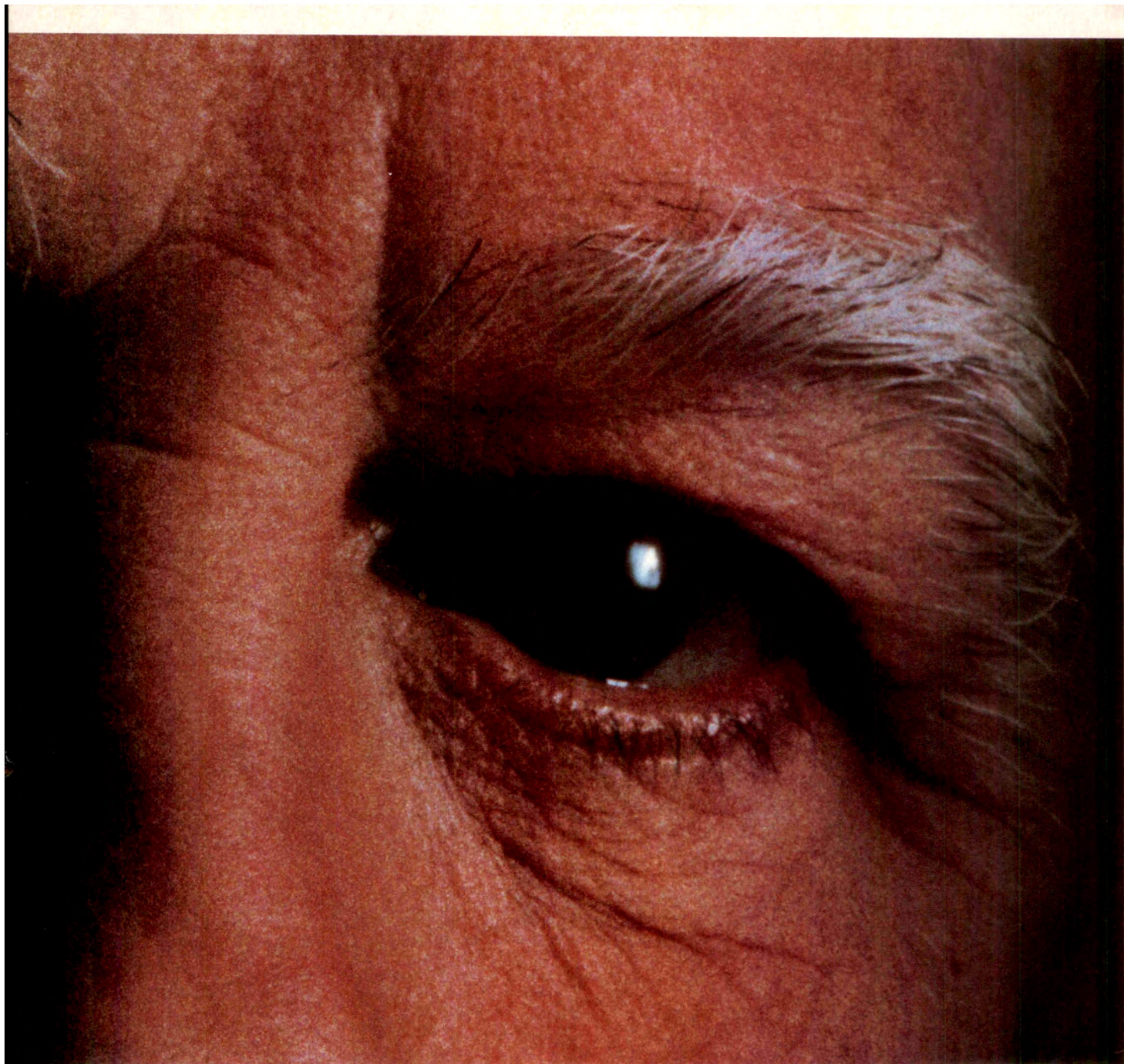
Loss of efficiency with age of several human physiologic functions.<sup>3</sup>



With BETOPTIC®S (beta: HCl) you can expect long-term maintenance of IOP reduction.<sup>4</sup> A superior pulmonary safety profile.<sup>5</sup> Minimal cardiovascular effects.<sup>6</sup> A very low incidence of respiratory side effects, including CNS effects.<sup>4</sup>

Doesn't it make sense to consider BETOPTICS when treating the elderly glaucoma patient?





BETOPTIC® S Sterile Ophthalmic Suspension has produced minimal effects in patients with reactive airway disease; exercise caution in treating patients with massive restriction of pulmonary function. Asthmatic attacks and pulmonary distress have been reported during betaxolol treatment. Although rechallenges of such patients with ophthalmic betaxolol have not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. Contraindicated in patients with sinus bradycardia, greater than a first-degree atrioventricular block, hypotension, hypovolemia, hypovolemic shock, overt cardiac failure or hypersensitivity to any component of this product. Use caution in treating patients with a history of cardiac failure or heart block. Observe patients receiving an oral beta blocker and BETOPTIC S Suspension for potential additive effect on the systemic effects of beta blockade. Exercise caution in patients receiving catecholamine-depleting drugs such as reserpine and adrenergic psychotropic drugs. BETOPTIC S Suspension has been well tolerated in a majority of patients. Discomfort of short duration upon instillation may be experienced. Systemic reactions have been reported rarely and a complete listing appears in prescribing information.

#### References:

1. Givens KT, Lee DA. Topical beta blockers for glaucoma: what clinicians should know. *Geriatric Medicine Today*. 1989;8:105-113.
2. Feigenbaum LZ. Geriatric medicine and the elderly patient. In: Schroeder SA, Krupp MA, Tierney LM, eds. *Current Medical Diagnosis and Treatment 1988*. Norwalk, Conn: Appleton & Lange; 1988:17-26.
3. Conrad KA, Bressler R. Drugs and advanced age. In: Modell W, ed. *Drugs of Choice, 1984-1985*. St Louis, Mo: CV Mosby Co; 1984:21-40.
4. Data on file, Alcon Laboratories, Inc.
5. Schoene RB, et al. Effects of topical betaxolol, timolol and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol*. 1984;97:86-92.
6. Atkins JM, et al. Cardiovascular effects of topical beta blockers during exercise. *Am J Ophthalmol*. 1985;99:173-175.

\*Beta-1 selectivity is not absolute.



**Betoptic® S**  
(betaxolol HCl)  
Sterile Ophthalmic  
Suspension, 0.25%

**S is for Strength of  
Suspension Technology**

Please see brief summary of prescribing information adjacent to this advertisement.  
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OPHTHALMIC  
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Fort Worth, Texas 76124



**BETOPTIC® S** (betaxolol HCl) 0.25% as base Sterile Ophthalmic Suspension

**DESCRIPTION:** BETOPTIC S Ophthalmic Suspension 0.25% contains betaxolol hydrochloride, a cardio-selective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation.

**INDICATIONS AND USAGE:** BETOPTIC S Ophthalmic Suspension 0.25% has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and ocular hypertension. It may be used alone or in combination with other intraocular pressure lowering medications.

**CONTRAINDICATIONS:** Hypersensitivity to any component of this product. BETOPTIC S Ophthalmic Suspension 0.25% is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

**WARNING:** Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with topical application of beta-adrenergic blocking agents. BETOPTIC S Ophthalmic Suspension 0.25% has been shown to have a minor effect on heart rate and blood pressure in clinical studies. Caution should be used in treating patients with a history of cardiac failure or heart block. Treatment with BETOPTIC S Ophthalmic Suspension 0.25% should be discontinued at the first signs of cardiac failure.

**PRECAUTIONS: General: Diabetes Mellitus.** Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia. **Thyrototoxicosis.** Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

**Muscle Weakness.** Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

**Major Surgery.** Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. **Pulmonary.** Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out. **Drug Interactions:** Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic. **Pregnancy: Pregnancy Category C.** Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS: Ocular:** In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, edema and anisocoria. **Systemic:** Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include: **Cardiovascular:** Bradycardia, heart block and congestive failure. **Pulmonary:** Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure. **Central Nervous System:** Insomnia, dizziness, vertigo, headaches, depression, and lethargy. **Other:** Hives, toxic epidermal necrolysis, hair loss, and glossitis.

**OVERDOSAGE:** No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. A topical overdose of BETOPTIC S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

**CAUTION: Federal (USA) Law Prohibits Dispensing Without a Prescription.**  
U.S. Patent Nos. 4,252,984; 4,311,708; 4,342,783; 4,911,920.

**Alcon®**  
OPHTHALMIC

ALCON LABORATORIES, INC.  
FORT WORTH, TEXAS 76134

**BSS PLUS®**

(Balanced Salt Solution Enriched with  
Bicarbonate, Dextrose and Glutathione)  
Sterile Intraocular Irrigating Solution

**DESCRIPTION:** BSS PLUS® is a sterile intraocular irrigating solution for use during all intraocular surgical procedures, even those requiring a relatively long intraocular perfusion time (e.g., pars plana vitrectomy, phacoemulsification, extracapsular cataract extraction/lens aspiration, anterior segment reconstruction, etc.).

The solution does not contain a preservative and should be prepared just prior to use in surgery.

**Part I:** A sterile 480 mL solution in a 500 mL single-dose bottle to which the Part II concentrate is added. Each mL of Part I contains: Sodium Chloride 7.44 mg, Potassium Chloride 0.395 mg, Dibasic Sodium Phosphate 0.433 mg, Sodium Bicarbonate 2.19 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection. DM-00

**Part II:** A sterile concentrate in a 20 mL single-dose vial for addition to Part I. Each mL of Part II contains: Calcium Chloride Dihydrate 3.85 mg, Magnesium Chloride Hexahydrate 5 mg, Dextrose 23 mg, Glutathione Disulfide (Oxidized Glutathione) 4.6 mg, in Water for Injection. DM-00

After addition of BSS PLUS Part II to the Part I bottle, each mL of reconstituted product contains: Sodium Chloride 7.14 mg, Potassium Chloride 0.38 mg, Calcium Chloride Dihydrate 0.154 mg, Magnesium Chloride Hexahydrate 0.2 mg, Dibasic Sodium Phosphate 0.42 mg, Sodium Bicarbonate 2.1 mg, Dextrose 0.92 mg, Glutathione Disulfide (Oxidized Glutathione) 0.184 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection.

The reconstituted product has a pH of approximately 7.4. Osmolality is approximately 305 mOsm.

**CONTRAINDICATIONS:** There are no specific contraindications to the use of BSS PLUS, however, contraindications for the surgical procedure during which BSS PLUS is to be used should be strictly adhered to.

**WARNINGS:** For IRRIGATION during ophthalmic surgery only. BSS PLUS is NOT for injection or intravenous infusion.

**PRECAUTIONS:** DO NOT USE BSS PLUS UNTIL RECONSTITUTED. Do not use Part I if it does not contain a vacuum. Do not use additives other than Part II. Do not use if Part I, Part II or the reconstituted solution is discolored or contains a precipitate. SINCE BSS PLUS IS INTENDED FOR INTRAOCULAR IRRIGATION, IT DOES NOT CONTAIN A PRESERVATIVE AND, THEREFORE, SHOULD NOT BE USED FOR MORE THAN ONE PATIENT. DISCARD ANY UNUSED SOLUTION SIX HOURS AFTER PREPARATION. Studies suggest that intraocular irrigating solutions which are iso-osmotic with normal aqueous fluids should be used with caution in diabetic patients undergoing vitrectomy since intraoperative lens changes have been observed.

There have been reports of corneal clouding or edema following ocular surgery in which BSS PLUS was used as an irrigating solution. As in all surgical procedures, appropriate measures should be taken to minimize trauma to the cornea and other ocular tissues.

**ADVERSE REACTIONS:** Postoperative inflammatory reactions as well as incidents of corneal edema and corneal decompensation have been reported. Their relationship to the use of BSS PLUS has not been established.

**OVERDOSAGE:** The solution has no pharmacological action and thus has no potential for overdosage. However, as with any intraocular surgical procedure, the duration of intraocular manipulation should be kept to a minimum.

U.S. Patent Nos. 4,443,432 and 4,550,022

**Alcon®**  
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Fort Worth, Texas 76134 USA

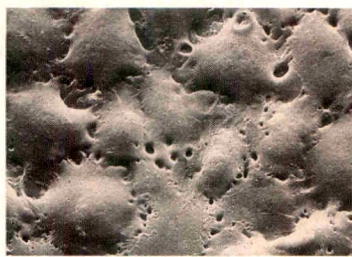
# BSS PLUS<sup>®</sup>

Sterile Intraocular Irrigating Solution

(Balanced Salt Solution Enriched with Bicarbonate, Dextrose, and Glutathione)

## Optimal perfusion diet for preserving endothelial health and integrity

***Only BSS PLUS solution delivers a complete  
intraocular perfusion diet***



**Incomplete perfusion diet –**  
Human cornea following 2 hours of  
in vitro endothelial perfusion with  
BSS solution. Marked swelling of  
endothelial cells is apparent.  
SEM magnification 1000x.<sup>1</sup>



**Complete perfusion diet –**  
The effect of **BSS PLUS** solution on  
human corneal endothelium after  
2 hours of in vitro perfusion. The result  
is a smooth endothelium with intact  
junctions. SEM magnification 1000x.<sup>1</sup>

Note: It is estimated that up to 8½ hours are  
required for a reforming solution to be replaced  
by normal aqueous humor in the postop eye.<sup>2</sup>

- A medium without equal for generating crystal clear corneas during *and* after surgery
- A unique and *complete* biological diet, containing:
  - *five essential ions*
  - *sodium bicarbonate* for optimal endothelial pump function and nutrient transport
  - *dextrose*, an energy source for cell metabolism and transparent corneas
  - *oxidized glutathione* for protection against surgically induced oxidative stress
- Optimal pH and osmolality



**Alcon<sup>®</sup>**  
SURGICAL

Innovation  
Without  
Compromise

#### References

1. Edelhauser HF. Intraocular irrigating solutions. In: Lamberts DW, Potter DE, eds. *Clinical Ophthalmic Pharmacology*. Boston, Mass: Little, Brown, 1987:431-444.
2. McDermott ML, et. al. Ophthalmic Irrigants: A Current Review and Update. *Ophthalmic Surgery*: October 1988, Vol. 19, No. 10:724-733.

Please see brief summary of prescribing information on the next page.

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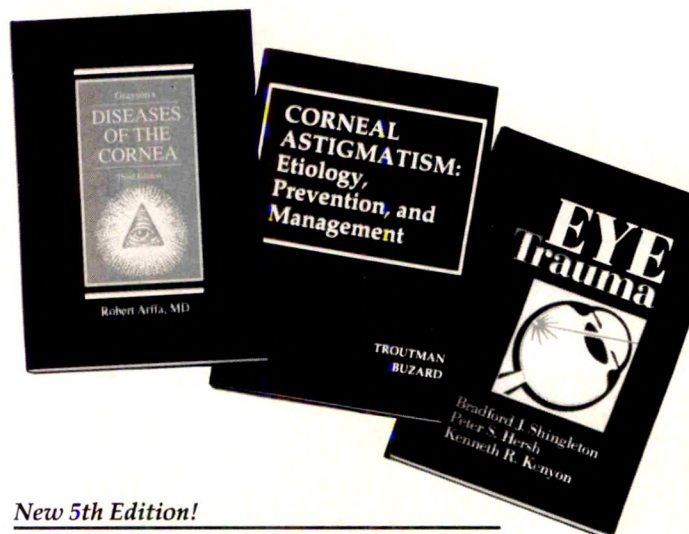
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## CATARACT SURGERY AND ITS COMPLICATIONS

Norman S. Jaffe, MD; Mark S. Jaffe, MD; and Gary F. Jaffe, MD

The newest edition of this popular reference has been updated to reflect the most up-to-date techniques in cataract surgery and the diagnosis and management of the myriad of complications which may develop. It retains the same outstanding format and features which made the previous editions successful yet adds information on the newest developments in silicone and hydrogel lens implants, apulsar bag fixation, single piece technology, 7mm optics, and histology, among other topics.

1990. 709 pages, 1,057 ills. and 16 color plates. (Book Code: 02885)

*New!*

## RETINAL DETACHMENT

Ronald G. Michels, MD; Charles P. Wilkinson, MD; and Thomas A. Rice, MD

This book focuses on retinal detachment, describing the current information available concerning its pathogenesis and management and comprehensively covers both diagnostic and surgical techniques regarding the disorder.

1990. 1,148 pages, 1,846 ills. (Book Code: 03417)

## THE GLAUCOMAS

Robert Ritch, MD; M. Bruce Shields, MD; and Theodore Krupin, MD

Written by internationally recognized authors, this stimulating two-volume set promises you the most comprehensive coverage on glaucoma currently available. It contains coverage of clinical diagnosis and management of the primary and secondary glaucomas; basic science, diagnostic techniques, and medical, laser, and surgical treatment of glaucomas.

1989. 1,369 pages, 1,200 ills. including 36 in 4 color plates - in two volumes. (Book Code: 04116)

*New 4th Edition!*

## OCULAR PATHOLOGY

David J. Apple, MD and Maurice Rabb, MD

This introductory text provides a correlation of clinical and pathologic findings of many aspects of ophthalmic pathology.

Features a new section on the Acquired Immunodeficiency Syndrome; expanded information on biotechnology as it affects the eye, e.g. pathology of the cornea caused by radial keratotomy and epikeratophakia, intraocular lenses, lasers, and on histopathology of the retina.

1991. 581 pages, 824 ills. with 167 in color. (Book Code: 00266)

**New!**

## **GLAUCOMA SURGERY**

John V. Thomas, MD, C. Davis Belcher III, MD, and Richard D. Simmons, MD

GLAUCOMA SURGERY provides comprehensive yet succinct coverage of the various operative procedures for the glaucoma, including filtering operations, aqueous drainage implants, iridectomy, goniotomy, trabeculotomy, and laser therapy.

October 1991. 512 pages, 486 ills. (Book Code: 05102)

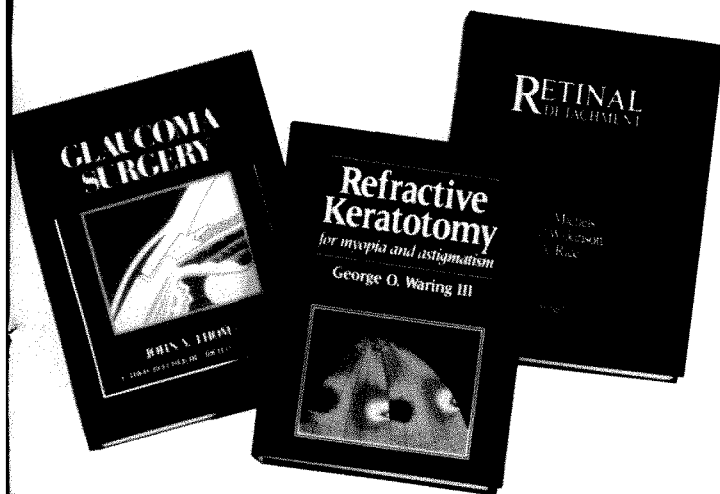
**New!**

## **REFRACTIVE KERATOTOMY FOR MYOPIA AND ASTIGMATISM**

George O. Waring III, MD, FACS; with 30 contributors.

Written by a leading specialist in the field, this new title carefully examines the innovative and controversial procedure of radial keratotomy. You'll find the facts you need to know on myopia and astigmatism, development of refractive keratotomy, patient selection and preplanning for refractive keratotomy, surgery, results, corneal biomechanics and computer modeling of refractive keratotomy, and more.

October 1991. Approx. 896 pages, 1,559 ills. (Book Code: 05349)



**New!**

## **A COLOUR ATLAS AND TEXTBOOK OF LENS IMPLANTATION**

PIERS PERCIVAL, MA, MB, BChir, FRCS, DO

The purpose of this new atlas is to explain, in pictorial form, the options now available, the reasoning behind change and the management of problems and complications.

1991. 256 pages, 600 ills. (Book Code: 21250)

**New!**

## **AUTOMATED STATIC PERIMETRY**

Douglas R. Anderson, MD

AUTOMATED STATIC PERIMETRY is a thorough, pragmatic, and up-to-date resource for those learning perimetry for the first time in a clinical setting where automated perimetry predominates.

Emphasis is on technical aspects of administering the automated test with skill; as well as on skillful interpretation of the result based on an understanding of the text.

October 1991. Approx. 336 pages, 220 ills. (Book Code: 06313)

**New!**

## **ATLAS OF CONTEMPORARY OPHTHALMIC SURGERY**

Henry M. Clayman, MD; with 18 contributors.

Organized by anatomic area, this new title is a comprehensive work that brings together all the various ophthalmic sub-specialty surgical procedures. It provides the information on such topics as surgical principles, anesthesia, cornea, lens, glaucoma, strabismus, vitreous, retina, photocoagulation, ophthalmic plastic surgery, orbit, and tumors—all in a concise outline format.

1990. 1,072 pages, 1,539 ills. (Book Code: 01136)

## **STEREOSCOPIC ATLAS OF MACULAR DISEASES: Diagnosis and Treatment, 3rd Edition**

J. Donald M. Gass, MD

1987. 840 pages in 2 volumes, 2,410 ills. Includes 20 stereo reels and viewer. (Book Code: 01752)

## **BECKER-SHAFFER'S DIAGNOSIS AND THERAPY OF THE GLAUCOMAS, 6th Edition**

H. Dunbar Hoskins, Jr., MD and Michael A. Kass, MD

The new 6th edition of this popular reference has been reorganized and totally rewritten with 25% more material to keep you up-to-date with the dynamic changes in the diagnosis and treatment of glaucoma. It features a wealth of new references, illustrations, and extensive use of tables and flow charts.

1989. 687 pages, 323 ills., including 6 color plates. 21 stereoscopic views in full color on 3 reels. (Book Code: 02453)

## **RETINA**

Stephen J. Ryan, MD; Thomas E. Ogden, MD, PhD; Andrew P. Schachat, MD; Robert P. Murphy, MD; Arnall Patz, MD; Bert M. Glaser, MD; and Ronald G. Michels, MD; with 164 expert contributors.

Bringing you over 150 informative chapters, this exciting new 3-volume reference presents the most detailed coverage of the diagnosis and treatment of retinal disease currently available. It's written by many leading authorities in the field—making it the definitive work on retina.

1989. 2,321 pages, in 3 volumes, 2,725 ills. including 27 color plates. (Book Code: 04241)

**New!**

## **THE 1991 YEAR BOOK OF OPHTHALMOLOGY**

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September 1991. Approx. 300 pages, 85 ills. (Book Code: 22135)

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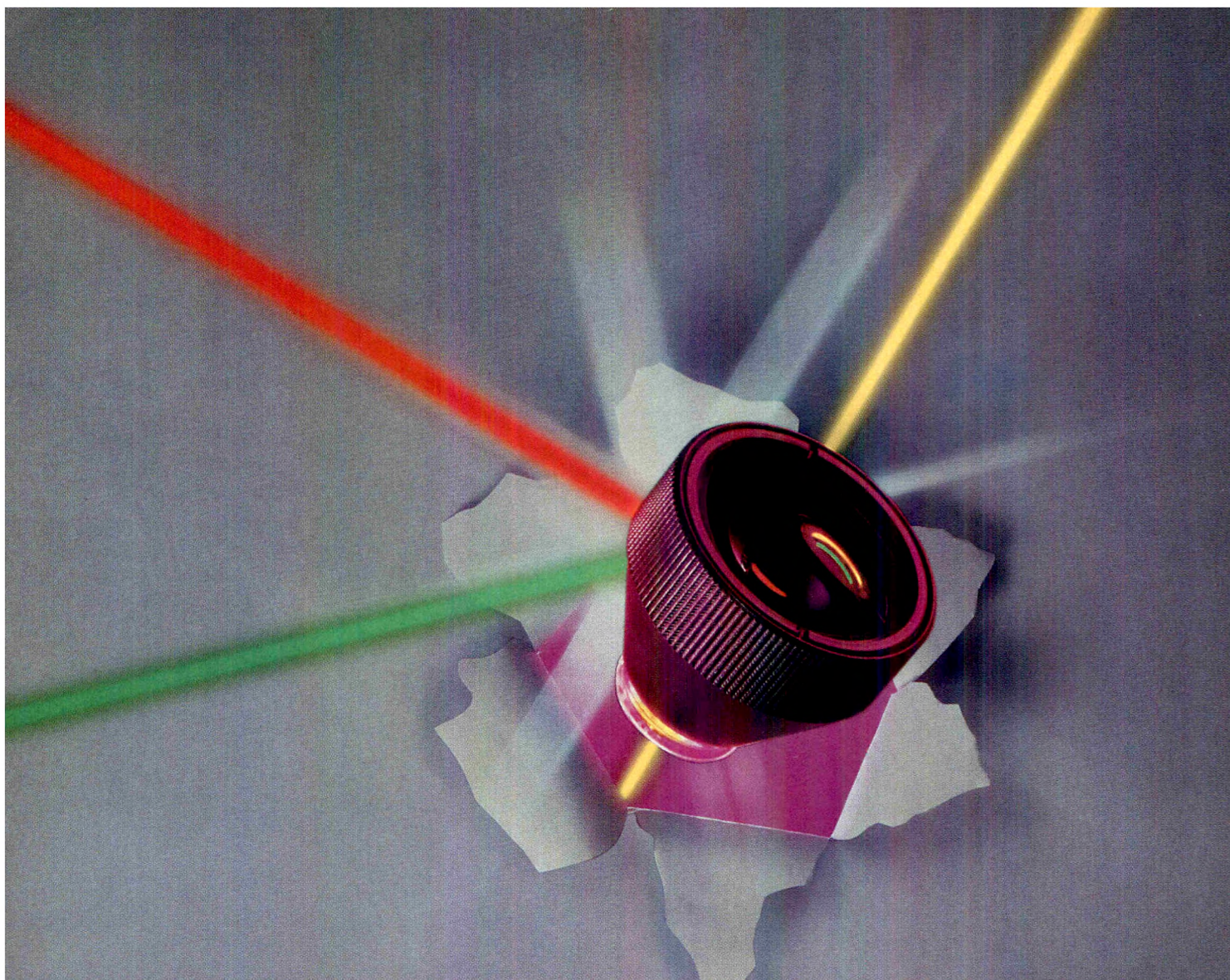
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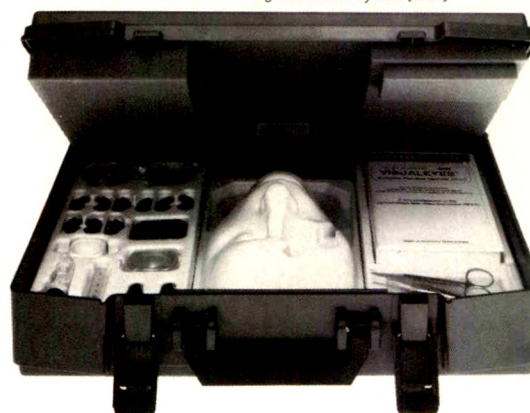
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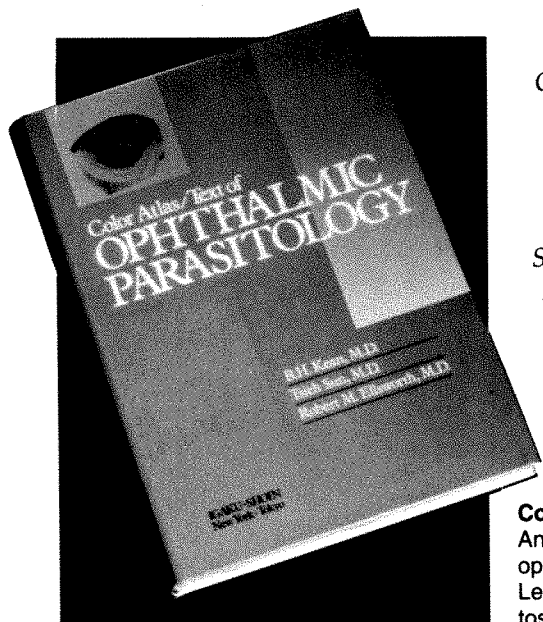
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*Chief, Division of Clinical Pathology, Department of Laboratories, North Shore University Hospital--Cornell University Medical College, Manhasset, NY and Professor of Clinical Pathology, Department of Pathology, Cornell University Medical College, New York, NY*

**Robert M. Ellsworth, M.D.**

*Professor of Ophthalmology, Cornell University Medical College and Attending Physician, The New York Hospital, New York, NY*

**Contents:** Abbreviations, Bibliography, Ophthalmic Glossary, General Introduction, Anatomy and Physiology of the Eye **Part I: Diseases Caused by Protozoa:** Toxoplasmosis, Terramebiasis, Entamebiasis, Malaria and Babesiosis, Giardiasis, Leishmaniasis, African Trypanosomiasis, American Trypanosomiasis, Pneumocystosis, Microsporidiosis **Part II: Diseases Caused by Nematodes:** Toxocariasis, Ascariasis, and Baylisascariasis, Onchocerciasis, Loiasis, Dirofilariasis, Bancroftian and Brugian Filariasis, Dracunculiasis, Thelaziasis, Gnathostomiasis, Angiostrongyliasis, Trichinosis **Part III: Diseases Caused by Cestodes:** Cysticercosis, Echinococcosis, Coenurosis, Sparganosis **Part IV: Diseases Caused by Trematodes:** Schistosomiasis, Paragonimiasis **Part V: Diseases Caused by Arthropods:** Ophthalmomyiasis **Index**

The movement of hundreds of thousands of people from one part of the world to another each year necessarily involves every physician in the practice of global medicine. This means that today's ophthalmologist is forced to include in his differential diagnosis the exotic virus, bacterium or parasite.

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Featuring 220 full-color illustrations in a large 8 1/2 by 11 inch format, this definitive reference, covering 26 parasitic disorders, will fill a true void in the literature. As a measure of the currentness of the new Atlas, it should be noted that many of the references are dated 1989 and 1990, and that it includes subjects that

were unknown only a few years ago.

Written by leading authorities in the field, this extensively illustrated full-color atlas is a crucial resource for the ophthalmologist. Use our convenient order form to obtain your copy of this invaluable diagnostic and therapeutic aid.

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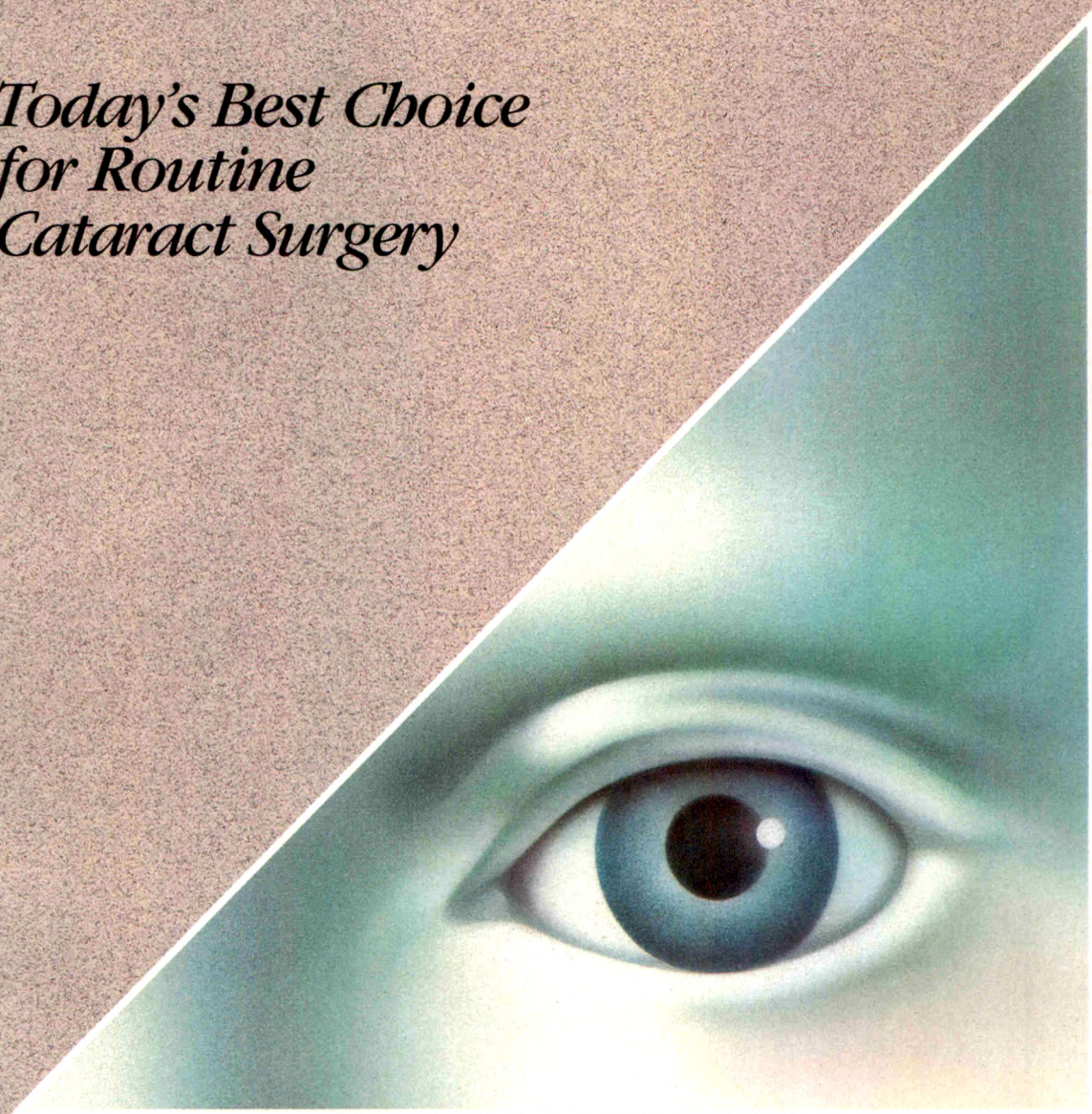
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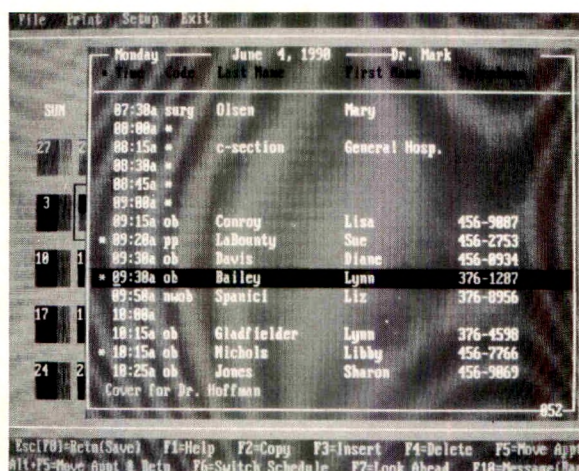


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### ► Computer Software

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DOCS, Inc. recently announced the initial release of its Professional Appointment Manager (PAM) for the medical office. The program is designed for scheduling appointments in either a single terminal or multi-user environment. PAM is a stand-alone program. It can be "hot-keyed" to operate on an integrated basis with any practice management program by using the new DOS version 5.0 upgrade. This allows users to go back and forth between PAM and another program without having to exit either one.

The program is capable of tracking appointments for multiple schedules, each with its own starting and ending times. PAM allows for varying time increments within each schedule. Messages as well as user-defined codes can be included for each appointment.

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### ► Lenses

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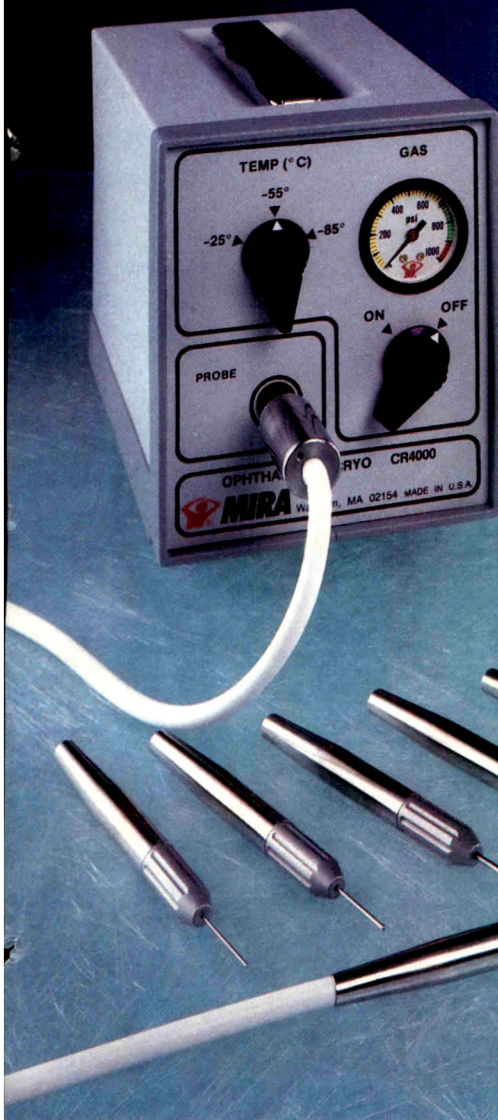
Ocular Instruments introduced four new rings for the Landers Vitrectomy Lens Ring System. The OLV-1/3s, Landers Three Strut Lens Ring features three struts which can be sutured to the sclera to hold the Landers Lenses in place. OLV-1/Is, Landers Three Strut Irrigating Lens Ring offers irrigation to allow easy irrigation of the cornea. Silicone tubing is included with the ring. OLV-1/N, Landers Notched Lens Ring features no struts, but has notches in the top of the ring for suture placement. Scleral depression is easier with this ring as no struts interfere. The OLV-1/IN version of the notched ring offers irrigation to allow easy irrigation of the cornea. Silicone tubing is included with the ring.







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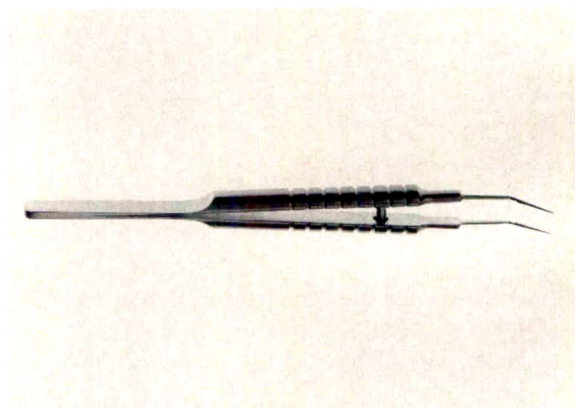
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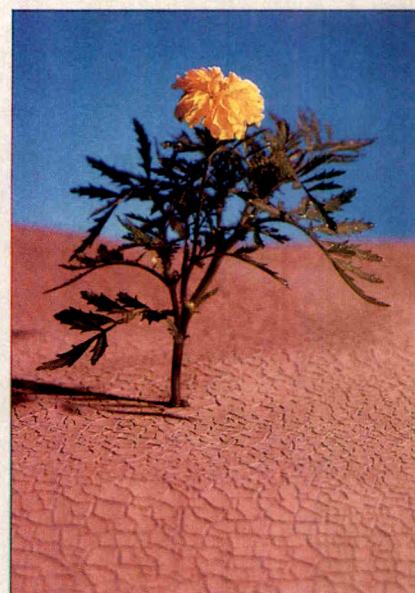
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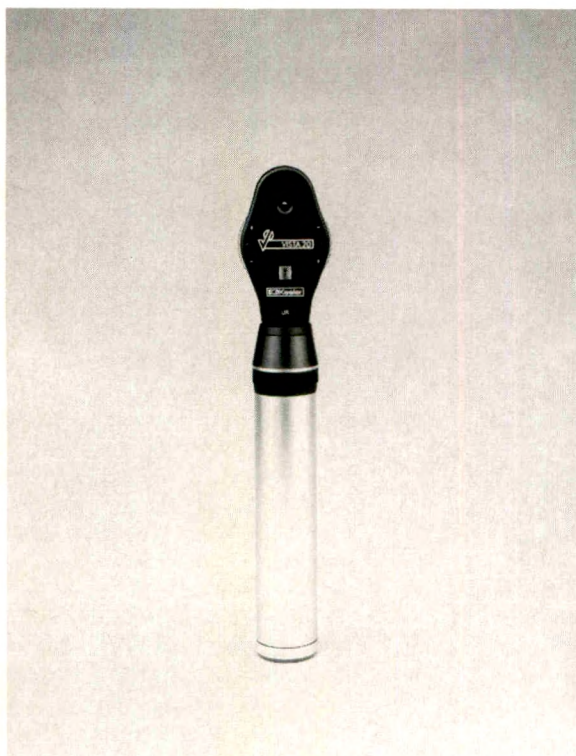
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## ► Diagnostic Instruments

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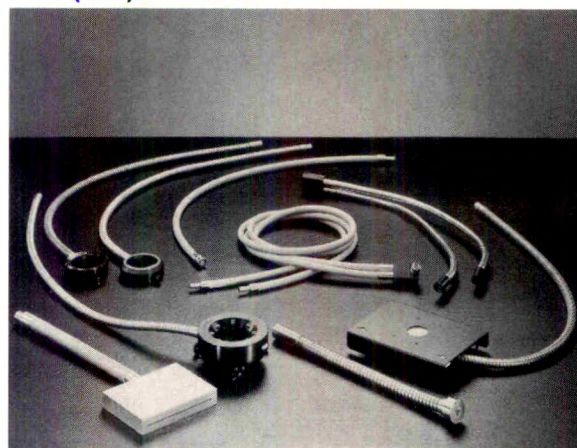
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## POSITIONS AVAILABLE

### TEXAS CORNEAL SPECIALIST WITH REFRACTIVE SURGERY EXPERIENCE:

Well-established, ten member group of sub-specialists in Fort Worth, seeks board certified/board eligible associate to join busy, multi-site, high pathology practice. Generous benefits and salary plus bonus. Flexible work schedule. This is an unusually good opportunity. Send C.V. and photograph to Laura Cadahia, Ophthalmology Associates, 308 South Henderson, Fort Worth, Texas 76104.

**VITREORETINAL SURGEON:** Growing multi-doctor medical and surgical retina only referral practice desires an associate leading to partnership. Practice is well established with excellent facilities and equipment. Quality retinal fellowship required. Reply with C.V. to Box 222 AJO.

**GENERAL OPHTHALMOLOGIST:** Prestigious, well-established ophthalmology practice in Chicago and northern suburbs looking for associate to begin immediately. Fellowship training in plastics, medical retina or cornea is desirable but not mandatory. Potential for possible partnership. Salary negotiable. Reply to Box 223 AJO.

**RETINAL SPECIALIST:** Marshfield Clinic wishes to recruit a BC/BE retina specialist with a primary interest in medical retina. The prospective physician would be joining a medical and a surgical retina specialist plus cornea, glaucoma, pediatric, and neuro-ophthalmology specialists and three general ophthalmologists. The Marshfield Clinic is a 350+ physician multispecialty group practice serving Central and Northern Wisconsin as well as the Upper Peninsula of Michigan. Complete practice setup, support staff, and a full complement of business office services are offered along with a competitive salary and excellent fringe benefits. This opportunity affords easy access to a wide variety of outdoor recreational activities, as well as safety and security for family living. For more information, send your C.V., or contact: Gary Pesicka, M.D., 1000 North Oak Avenue, Marshfield, WI 54449 or call (715) 387-5236.

### ACADEMIC OPHTHALMOLOGISTS Pediatric Ophthalmologist—Geneticist Retina and Vitreous Surgeon

The University of Nebraska College of Medicine, Department of Ophthalmology, is seeking two full-time academic ophthalmologists. A strong commitment to resident, medical student teaching, and research is essential. Requirements include completion of a satisfactory residency and American Board of Ophthalmology eligibility or certification. Must have documented prior teaching and research experience. Salary and rank commensurate with education and experience. Health Professions (tenure-leading) appointment contract with potential for renewal. Positions available immediately. Send C.V. to:

Michael E. Yablonski, M.D., Ph.D.  
 Professor and Chairman  
 Department of Ophthalmology

University of Nebraska Medical Center  
 600 South 42nd Street, Omaha, NE 68198-5540  
 (402) 559-4276 FAX: (402) 559-5514

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**OPHTHALMOLOGISTS—MARSHFIELD CLINIC**

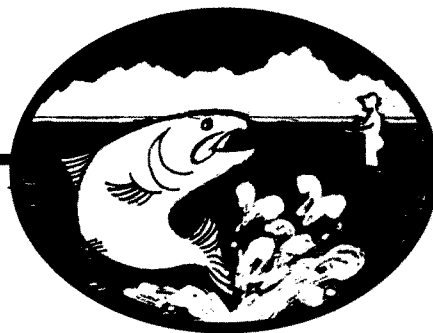
A 400 physician multispecialty group practice is seeking BE/BC ophthalmologists to join expanding regional centers in **ASHLAND** and **RICE LAKE, WISCONSIN**. These are beautiful, wooded Wisconsin areas with an abundance of lakes, rivers and streams. Each is ideally suited for physicians seeking to combine professional excellence in a Midwest, family-oriented location offering exceptional four-season recreational activities. **Ashland** is a community of 9,000 located on the southern shores of Lake Superior. This is a single-specialty group seeking a third partner. **Rice Lake** is a lakeside community of 8,500 people located less than 2½ hours northeast of Minneapolis/St. Paul. This is a growing multispecialty group practice of 18 physicians. Wisconsin consistently leads the nation in ACT scores and the school systems in these communities are excellent. Each opportunity offers a superlative life-style. Each has its own special qualities with more attractive features relative to individual needs and preferences. The initial total compensation package is valued in excess of \$200,000. If this combination of professional excellence and life-style made possible through the backup resources of a leading medical center in conjunction with the uncommon, varied beauty of Wisconsin's land and lakes sounds interesting to you, please send C.V. and references to David L. Draves, Director Regional Development, 1000 North Oak Avenue, Marshfield, WI 54449, or call 1-800-825-2345, extension 5376.

**VITREO-RETINAL SURGEON:** Dynamic medical/surgical retina vitreous only practice in large mid-western city seeks fellowship trained vitreoretinal surgeon. Academic affiliation available. BE/BC. Send C.V. to Box 227 AJO.

**The University of Maryland School of Medicine** seeks nominations for a Chairman for the Department of Ophthalmology. The School of Medicine and 747-bed University Hospital share a campus with six other professional schools and a new 324-bed VA Hospital with a large outpatient census. The campus forms the western-most border of downtown Baltimore's renowned Inner Harbor. The Chairman's responsibility includes programs in the Medical School, the University of Maryland Hospital, the adjacent VA Medical Center and the Faculty Practice Building. A highly competitive residency program is in place. Nominees should hold the M.D. degree or equivalent and be Board certified in Ophthalmology with established credentials in education, research, clinical service and have demonstrated academic leadership ability. Applicants should submit a C.V. and names of three references by November 1, 1991 to Kenneth P. Johnson, MD, Search Committee Chairman c/o Dean's Office, University of Maryland School of Medicine, 655 West Baltimore Street, Baltimore, Maryland 21201. The University of Maryland is an Equal Opportunity/Affirmative Action Employer.

**POSITIONS AVAILABLE** in oculoplastic and orbital surgery, glaucoma, retina, general ophthalmology, and pediatric ophthalmology at Cleveland and Ft. Lauderdale locations. Candidates require M.D. degree from accredited U.S. medical school, completion of approved ophthalmic residency training program in U.S. hospital. Send C.V. to: Froncie A. Gutman, M.D., Chairman, Dept. of Ophthalmology, Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Ave., Cleveland, OH 44195-5024. An EEO/AA employer.

**GENERAL OPHTHALMOLOGIST**—Central New Jersey group seeking a board eligible or certified ophthalmologist for immediate partner-



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OPHTHALMOLOGIST-IN-CHIEF  
THE DETROIT MEDICAL CENTER HOSPITALS**

Wayne State University School of Medicine, the Kresge Eye Institute, The Detroit Medical Center and its member hospitals, are seeking an outstanding clinician, researcher and administrator to serve as Professor and Chair of the Department of Ophthalmology, Director of the Kresge Eye Institute at the Wayne State University School of Medicine and the Ophthalmologist-in-Chief of the Detroit Medical Center. The individual we seek is expected to plan, manage and implement academic, research and clinical programs that 1) enhance the professional and scholarly growth of the Department, the Institute, and the hospitals of the Medical Center; 2) provide leadership to the faculty and the attending staff at the various hospitals within the Medical Center; and, 3) continue and expand upon the hospitals' commitment to the community. Applicants should have attained national and international stature in the field of Ophthalmology, and demonstrate a record of excellence in scholarship, clinical service, and academic administration. A strong basic science background is desirable. The incumbent will have overall responsibility for medical students and post-graduate education in Ophthalmology at the Wayne State University School of Medicine, be expected to promote the development of research programs of appropriate breadth and depth for a university department of national and international stature and to organize the Ophthalmologic resources of the Kresge Eye Institute and the system hospitals toward a broadly based academic and clinical unit.

Interested applicants should forward a letter of application and an updated curriculum vitae along with the names of three references by September 30, 1991, to:

**Robert P. Lisak, M.D., Professor and Chairman of Neurology  
Wayne State University School of Medicine  
University Health Center-6E  
4201 St. Antoine, Detroit, Michigan 48201**

*Wayne State University and the Detroit Medical Center Hospitals are  
equal opportunity/affirmative action employers.*



**GLAUCOMA**

Full-time position for a glaucoma specialist with opportunities for clinical research and teaching in a very busy not-for-profit setting. Candidate must be BC or BE, and at least one year of subspecialty training in glaucoma.

Practice is located in a modern, state-of-the-art equipped facility in the scenic Black Hills area of South Dakota. The facility includes subspecialists in retina, pediatrics, neuro, plastics, cornea and anterior segment. This regional center serves patients from a five state area, and provides services at fifteen satellite locations.

Please forward letters of application and C.V. to:

Joseph Dillenburger, Executive Director  
Black Hills Regional Eye Institute  
2800 South Third Street  
Rapid City, SD 57701

**VITREO-RETINAL SURGEON:** Medical and surgical, retina only, referral practice desires third associate (retinal fellowship trained) leading to partnership. **State of the art vitreo-retinal practice.** Reply with C.V., and photo to Box 228 AJO.

**RETINA SPECIALIST:** Established Multi-specialty ophthalmology group, located on central Florida's beautiful gulf coast, seeks fellowship-trained retina surgeon to build on established base. A caring well-trained staff, state of the art equipment and modern offices await the empathetic, motivated and confident person we are seeking. Some general ophthalmology required until practice is fully developed. Salary, incentive, and partnership opportunity available at the end of 2 years. Send C.V. and photograph to Box 229, AJO.

**PEDIATRIC OPHTHALMOLOGIST:** Second, full-time, academic pediatric ophthalmologist needed for expanding department at children's hospital. BE/BC, fellowship trained. Clinical, research, and teaching responsibilities. Position available immediately or will discuss starting date. Contact: David J. Schanzlin, M.D., Chairman, Department of Ophthalmology, Saint Louis University School of Medicine, Bethesda Eye Institute, 3655 Vista, St. Louis, MO 63110.

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**GLAUCOMA SPECIALIST/MARSHFIELD CLINIC**

Full specialty Ophthalmology Department, in a large multi-specialty group practice, is seeking a fellow-trained glaucoma specialist. Qualified physician would join a nine member department with one existing glaucoma specialist. Competitive salary, excellent fringe benefits, with equipment and support staff provided. Large referral base with nearest glaucoma specialist more than 100 miles distant. Area offers a wide variety of outdoor recreational opportunities. For more information, send C.V. or contact Dr. Richard Patchett, 1000 North Oak Avenue, Marshfield, WI 54449, or call (715) 387-5236.

**PEDIATRIC OPHTHALMOLOGIST POSITION** is currently available at the level of Assistant Professor in the Department of Ophthalmology, University of North Carolina, Chapel Hill, North Carolina. Qualifications are clinical expertise, a strong commitment to teaching and resident training, and a strong background in laboratory and/or clinical research. Requirements include an approved ophthalmic residency program, completion of postgraduate training (fellowship in pediatric ophthalmology and a second fellowship in another recognized ophthalmic specialized area), Board certification or eligibility, and eligibility for licensure in North Carolina. The University of North Carolina is an Equal Opportunity/Affirmative Action Employer. Academic rank and salary are negotiable. Contact David Eifrig, M.D., Professor and Chairman, Department of Ophthalmology, University of North Carolina School of Medicine, CB# 7040, Chapel Hill, North Carolina 27599, Telephone (919) 966-5296. Fax (919) 966-1908.

**OPHTHALMOLOGIST:** to join busy surgical practice in rural Pennsylvania. Generous salary with future partnership for intelligent, educable, board eligible ophthalmologist with strong surgical orientation. Reply to Box 230 AJO.

**OPHTHALMOLOGIST** desiring long-term association. BC/BE general ophthalmologist; subspecialty training and/or previous practice experience desirable but not mandatory. Join existing practice expanding to 3 ophthalmologists, largely secondary and tertiary care. Excellent office/ASC, hospital facilities and staffs. Attractive family-oriented community of 100,000 nestled in Yellowstone Valley, 1 hour from Rocky Mountains. Drawing area 250-350,000. Salary with incentive. Progressing to full partnership. Send C.V. and references. Billings Eye Clinic, 34 Heatherwood Lane, Billings, MT 59102.

**BE/BC OPHTHALMOLOGIST MID-OHIO VALLEY:** Forty-year old solo practitioner with practice limited to cataracts, glaucoma and medical retina seeks associate leading to partnership. Send resume, photo and references to Richard Johns, M.D., 7 Rosemar Circle, Parkersburg, WV 26104.

**POSITIONS WANTED**

**MEDICAL RETINAL SPECIALIST** wants to join large multi-specialty or retina group. Fellowship trained with experience in all aspects of medical retina including electrophysiology. Prefer east coast but not geographically limited. Please send to Box 228 AJO.

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## EQUIPMENT FOR SALE

**FOR SALE: OCTOPUS 2000 AUTOMATED PERIMETER.** Price negotiable. Reply: Gene Driscoll, 308 S. Henderson, Fort Worth, Texas 76104.

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### PLEASE NOTE

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### BRIEF SUMMARY

**CONTRAINDICATIONS:** Hypersensitivity to any component of this product.

OPTIPRANOLOL™ Ophthalmic Solution is contraindicated in patients with bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease; symptomatic sinus bradycardia; greater than a first degree atrioventricular block; cardiogenic shock; or overt cardiac failure.

**WARNINGS:** As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. Thus, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely, death in association with cardiac failure, have been reported following topical application of beta-adrenergic blocking agents (see CONTRAINDICATIONS).

Since OPTIPRANOLOL™ Ophthalmic Solution had a minor effect on heart rate and blood pressure in clinical studies, caution should be observed in treating patients with a history of cardiac failure. Treatment with OPTIPRANOLOL™ Ophthalmic Solution should be discontinued at the first evidence of cardiac failure.

OPTIPRANOLOL™ Ophthalmic Solution, or other beta blockers, should not, in general, be administered to patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity (see CONTRAINDICATIONS). However, if the drug is necessary in such patients, then it should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta<sub>2</sub> receptors.

**PRECAUTIONS:** General: Because of potential effects of beta-adrenergic receptor blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with OPTIPRANOLOL™ Ophthalmic Solution, alternative therapy should be considered.

Some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents in patients undergoing elective surgery. If necessary during surgery, the effects of beta-adrenergic receptor blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levaterenol.

While OPTIPRANOLOL™ Ophthalmic Solution has demonstrated a low potential for systemic effect, it should be used with caution in patients with diabetes (especially labile diabetes) because of possible masking of signs and symptoms of acute hypoglycemia.

Beta-adrenergic receptor blocking agents may mask certain signs and symptoms of hyperthyroidism, and their abrupt withdrawal might precipitate a thyroid storm.

Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness).

Risk of anaphylactic reaction: While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

**Drug Interactions:** OPTIPRANOLOL™ Ophthalmic Solution should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally, because of the potential for additive effects on systemic beta-blockade.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia.

Caution should be used in the coadministration of beta-adrenergic receptor blocking agents, such as metipranolol, and oral or intravenous calcium channel antagonists, because of possible precipitation of left ventricular failure, and hypotension. In patients with impaired cardiac function, who are receiving calcium channel antagonists, coadministration should be avoided.

The concomitant use of beta-adrenergic receptor blocking agents with digitalis and calcium channel antagonists may have additive effects, prolonging arterioventricular conduction time.

Caution should be used in patients using concomitant adrenergic psychotropic drugs.

**Ocular:** In patients with angle-closure glaucoma, the immediate treatment objective is to re-open the angle by constriction of the pupil with a miotic agent. OPTIPRANOLOL™ Ophthalmic Solution has little or no effect on the pupil, therefore, when it is used to reduce intraocular pressure in angle-closure glaucoma, it should be used only with concomitant administration of a miotic agent.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime studies with metipranolol have been conducted in mice at oral doses of 5, 50, and 100 mg/kg/day and in rats at oral doses of up to 70 mg/kg/day. Metipranolol demonstrated no carcinogenic effect. In the mouse study, female animals receiving the low, but not the intermediate or high dose, had an increased number of pulmonary adenomas. The significance of this observation is unknown. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, metipranolol was nonmutagenic.

Reproduction and fertility studies of metipranolol in rats and mice showed no adverse effect on male fertility at oral doses of up to 50 mg/kg/day, and female fertility at oral doses of up to 25 mg/kg/day.

**Pregnancy: Pregnancy Category C:** No drug related effects were reported for the segment I teratology study in fetal rats after administration, during organogenesis, to dams of up to 50 mg/kg/day. OPTIPRANOLOL™ Ophthalmic Solution has been shown to increase fetal resorption, fetal death, and delayed development when administered orally to rabbits at 50 mg/kg during organogenesis.

There are no adequate and well-controlled studies in pregnant women. OPTIPRANOLOL™ Ophthalmic Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether OPTIPRANOLOL™ Ophthalmic Solution is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when OPTIPRANOLOL™ Ophthalmic Solution is administered to nursing women.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** In clinical trials, the use of OPTIPRANOLOL™ Ophthalmic Solution has been associated with transient local discomfort.

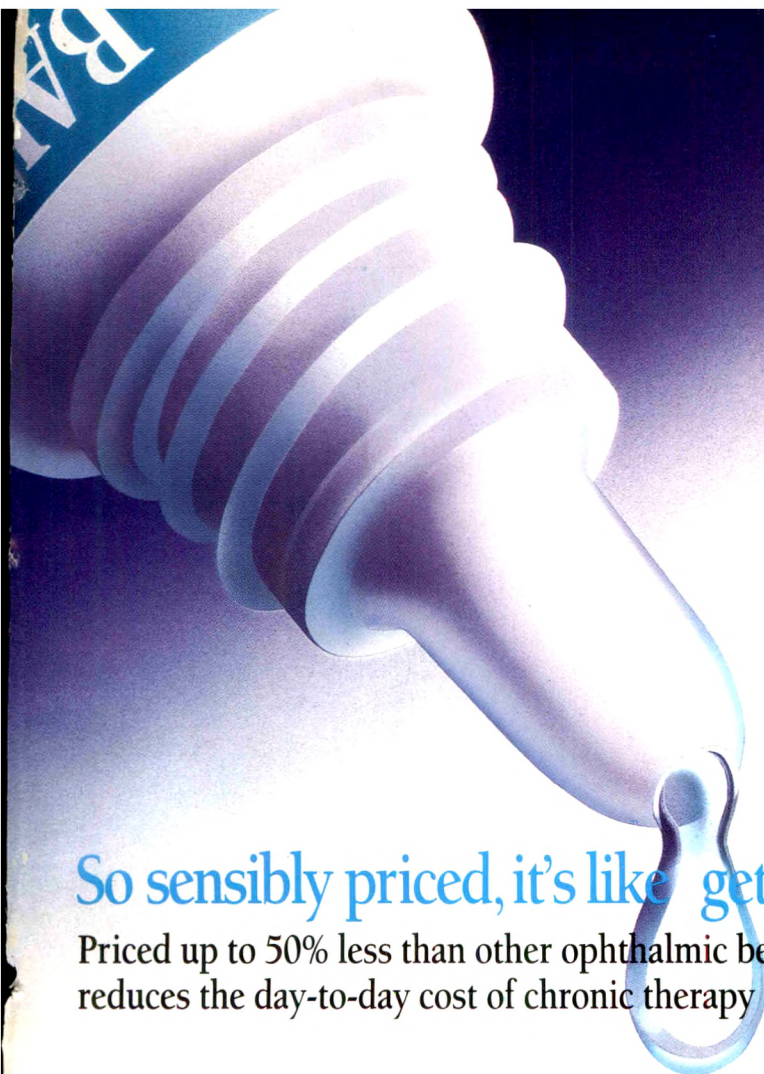
Other ocular adverse reactions, such as conjunctivitis, eyelid dermatitis, blepharitis, blurred vision, tearing, browache, abnormal vision, photophobia, and edema have been reported in small numbers of patients, either in U.S. clinical trials or from post-marketing experience in Europe.

Other systemic adverse reactions, such as allergic reaction, headache, asthenia, hypertension, myocardial infarct, atrial fibrillation, angina, palpitation, bradycardia, nausea, rhinitis, dyspnea, epistaxis, bronchitis, coughing, dizziness, anxiety, depression, somnolence, nervousness, arthritis, myalgia, and rash have also been reported in small numbers of patients.

**OVERDOSAGE:** No information is available on overdosage of OPTIPRANOLOL™ Ophthalmic Solution in humans. The symptoms which might be expected with an overdose of a systemically administered beta-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure. Revised 3/90

**REFERENCES:** 1. Data on file. Bausch & Lomb Pharmaceutical Division. 2. von Denffer H. Efficacy and tolerance of metipranolol—Results of a multi-center long-term study. In: Merte H-J, ed. *Metipranolol: Pharmacology of Beta-blocking Agents and Use of Metipranolol in Ophthalmology*. Vienna: Springer-Verlag, 1983: 121-125. 3. Dausch D, Brewitt H, Edelhoff R. Metipranolol eye drops—Clinical suitability in the treatment of chronic open angle glaucoma. In: Merte H-J, ed. *Metipranolol: Pharmacology of Beta-blocking Agents and Use of Metipranolol in Ophthalmology*. Vienna: Springer-Verlag, 1983: 132-147. 4. OptiPranolo!™ Package Insert.

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\*Cost is to the pharmacist based on Average Wholesale Price listings in Medi-Span, March, 1991, and First Data Bank Price Alert, February 15, 1991.

□ Well tolerated, with a low potential for systemic side effects<sup>2-5</sup>

□ Effectively reduces IOP an average of 20–26% in patients with IOP greater than 24mm Hg<sup>1-4</sup>

□ Safe in concomitant therapy with pilocarpine, epinephrine, and acetazolamide<sup>1</sup>

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Effective IOP reduction in patients with chronic open angle glaucoma and ocular hypertension

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References: 1. Data on file. Bausch & Lomb Pharmaceutical Division, Inc. 2. Von Denffer H. Efficacy and tolerance of metipranolol — results of a multi-center long-term study. In: Merte H-J, ed. *Metipranolol: Pharmacology of Beta-blocking Agents and Use of Metipranolol in Ophthalmology*. Vienna: Springer-Verlag; 1983: 121-125. 3. Dausch D., Brewitt H., Edelhoff R. Metipranolol eye drops — clinical suitability in the treatment of chronic open angle glaucoma. In: Merte H-J, ed. *Metipranolol: Pharmacology of Beta-blocking Agents and Use of Metipranolol in Ophthalmology*. Vienna: Springer-Verlag; 1983: 132-147. 4. Rolando M., Murialdo V., Dolci A., Sanfelici G., Calabria G. *New Beta Blockers: Comparison of Efficacy Versus Timolol Maleate*. Glaucoma 1989; 11:27-30. 5. OptiPranolol™ Package Insert.

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